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Martinus Cornelius Maria van Beers

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Improving cognition and healthy lifestyle behavior in chronic obstructive pulmonary disease

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Martinus Cornelius Maria van Beers

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Promotor

Prof. dr. A. M. W. J. Schols

Co-promotor

Dr. H. R. Gosker

Beoordelingscommissie

Prof. dr. A. Jansen (voorzitter)

Prof. dr. L. C. P. G. M. de Groot (Wageningen University)

Dr. S. Köhler

Prof. dr. D. van de Mheen (Tilburg University)

Prof. dr. G. Wesseling

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Chapter 1

General Introduction

Chronic obstructive pulmonary disease

Chronic obstructive pulmonary disease (COPD) is a common and preventable chronic disease which is characterized by airflow limitation that is usually progressive (1). An estimated 299 million people worldwide suffered from the disease in 2017 (2) and it caused 3 million deaths in 2016, making it the third most common cause of death worldwide (3). Tobacco smoking and exposure to air pollution, toxic gases and biomass fuel emission are the most common risk factors for developing COPD (4).

The pathophysiology in the lungs primarily consists of chronic bronchitis (airway inflammation) and emphysema (destruction of the small airways) (1), but COPD is highly heterogeneous. Various systemic manifestations outside the lungs and airways are common. These include cardiovascular disease (5), musculoskeletal impairment (6), cachexia (7), sarcopenia (8), metabolic syndrome (MetS) (9), anxiety and depression (10, 11) and cognitive abnormalities (e.g., 12, 13). The entire constellation of COPD manifestations contributes to increased disease burden, worsened health status and functional performance, increased hospitalization and mortality risk and higher healthcare costs (14-16).

COPD is incurable but can be treated. Smoking cessation is the most effective prevention as well as treatment strategy. The current guidelines recommend additional pharmacological treatment using a combination of long-acting muscarinic antagonists and β2-agonists, combined in severe cases with inhaled corticosteroids (1). Patients who remain symptomatic despite optimal treatment and/or those with complex pathology (such as poor lung function, high burden of comorbidities, a poor functional or nutritional status and/or frequent exacerbations) can be referred to pulmonary rehabilitation (PR) (17) or in very specific cases be eligible for lung volume-reducing endoscopic or surgical intervention (1).

Pulmonary rehabilitation

PR is defined as "a comprehensive intervention based on a thorough patient assessment followed by patient-tailored therapies that include, but are not limited to, exercise training, education and behavior change, designed to improve the physical and psychological condition of people with chronic respiratory disease and to promote the long-term adherence to health-enhancing behaviors" (17).

PR is one of the most effective interventions to improve the health status of patients with COPD. Exercise capacity and health-related quality of life can

increase significantly over the course of a PR program (18). However, the long-term efficacy of PR has not been investigated yet. This is relevant because PR-induced gains translate only poorly into a healthier lifestyle, such as more physical activity, after PR (18). Moreover, specific subgroups of patients could benefit from specific additional treatments, such as nutritional supplementation (19, 20). These considerations were the main rationale to design the randomized, double-blind, placebo-controlled NUTRAIN trial. This trial investigated the efficacy and cost-effectiveness of a multimodal nutritional management strategy, consisting of nutritional supplementation and dietary counseling, in COPD patients with low muscle mass during a 4-month outpatient PR program and in the 8-month maintenance phase thereafter. The results of the initial 4-month phase were published earlier (21); the efficacy and cost-effectiveness of the overall strategy are reported in Chapter 2 of this thesis.

Nutritional supplementation did not improve quadriceps muscle strength during the initial PR phase of the NUTRAIN trial. Interestingly, however, supplementation prevented declines in daily physical activity (21). This dissociation between physical capacity and activity, combined with positive effects on plasma micronutrient status and quality of life (21) led to the hypothesis that mechanisms affecting cognitive performance and mental health might be involved.

The main aim of this thesis was therefore to investigate determinants of cognitive performance in patients with COPD and the potential efficacy of working memory training (WMT) next to motivational regulations in increasing patients' adherence to a healthy lifestyle.

Motivational regulations as determinants of PR-induced health improvement

The central tenet of self-determination theory (SDT) is that motivation is the key determinant of behavior (22). SDT conceptualizes motivation as a quantitative construct (i.e., one can be more or less motivated towards something), but it also distinguishes six qualitatively different motivational regulations which can differentially drive behavior. These regulations can be placed on a continuum, ranging from being more intrinsic (performing a behavior because of the enjoyment derived from doing it) to more extrinsic forms of motivation (performing a behavior because of some secondary rewards associated with it) (23). Although all motivational regulations can drive behavior, a larger reliance on more intrinsic regulations as opposed to more extrinsic ones is generally considered beneficial.

Intrinsic behavioral regulation is more stable and enduring and benefits one's wellbeing more compared to controlled regulation (24).

Because of their important role in determining behavior, motivational regulations could be the key to ensure PR-induced gains translate into a longer-term healthy lifestyle after the PR program is completed and the associated external support is not present anymore. If motivational regulations are related to healthy lifestyle behaviors before, during and/or after a PR program, they could be used as predictors of adherence to healthy lifestyle behaviors, or even as interventional targets to improve this adherence. Earlier studies have already shown that motivational interviewing, which is a psychological counseling technique based on SDT, can increase medication adherence (25, 26), exercise compliance (26) and health-related quality of life (26-28) and can reduce hospitalization rates (26, 27) in patients with COPD.

Chapter 3 investigates the value of motivational regulations to predict the carry-over of PR-induced healthy lifestyle gains into a healthier lifestyle.

Cognitive functioning

Cognitive functioning involves any brain function required for perceiving, registering, storing, retrieving and using information from the environment in order to be able to adapt one's behavior to novel situations (29). Cognitive functioning is not a unitary construct but consists of different functions, such as memory, attention, self-control, task switching, inhibition and many more. Furthermore, 'lower' functions can be distinguished from 'higher' ones, with the lower functions (e.g., sensory processing, attention and language abilities) serving as the foundation for the higher ones (e.g., cognitive flexibility, self-control and problem-solving) (29).

Executive functions encompass various higher-order cognitive functions involved in behavioral control. Specifically, inhibition, task switching and working memory (WM) are generally considered to jointly constitute executive functioning (30). Inhibition refers to the ability to override or interrupt undesired behavioral responses (31), and enables to focus on one particular thing instead of being distracted by other items in our environment. Task switching is the ability to quickly switch one's focus from one item to another, and to change demands and priorities (30). This ability makes it possible to avoid behavioral interference from previous tasks, thereby preventing perseveration when a behavioral strategy does not lead to attaining a certain goal (anymore) (32). Finally, WM refers to the ability

to temporarily keep important information in mind, enabling the information to be mentally manipulated (33). WM is also involved in the ability to focus one's attention (34) and to actively keep a representation of long-term goals (35).

There are large inter-individual differences in cognitive functioning. One person's WM might be very strong (for instance if he or she is able to remember and immediately reproduce an entire phone number after hearing it once), whereas in someone else it might be very poor. Likewise, there are large intra-individual differences in cognitive functioning. Someone might simultaneously have a very strong long-term memory but very poor inhibition skills.

Measuring cognitive performance

Cognitive performance can be quantified by using standardized cognitive tests. Because so many different cognitive domains exist, countless tests have been developed to gauge people's performance on those domains. Cognitive tests can be distinguished into screening tools and comprehensive neuropsychological assessment batteries (36).

Screening tools, such as the Mini-Mental State Examination (MMSE) (37), the Montreal Cognitive Assessment (MoCA) (38) and the Addenbrooke's Cognitive Examination-Revised (ACE-R) (39), can be administered relatively quickly (often within 10 to 15 minutes), are generally narrow in scope, and they do not have a diagnostic purpose (36). Screening tools are used in clinical practice to obtain a quick overview of the cognitive performance of a person presenting with memory problems and to determine whether he or she can benefit from referral for more extensive cognitive assessment.

More detailed assessment is conducted using comprehensive neuropsychological test batteries (36), such as the Cambridge Neuropsychological Test Automated Battery (CANTAB). It takes more time and effort to administer such batteries, but their broader scope (i.e., their ability to measure more cognitive domains more thoroughly) and their higher sensitivity to detect CI are large advantages compared to screening tools (36). Therefore, such batteries can be used for diagnostic purposes in a clinical setting (36) and as valid and reliable outcome measures for clinical trials in a scientific setting (40).

Cognitive impairment in COPD and its consequences

The large impact of COPD on the brain and cognitive functioning has long been under-recognized, but the awareness for the neuropsychological consequences

of COPD has increased in recent years (e.g., 12, 13). The prevalence of CI is significantly higher in patients with COPD compared to non-COPD controls. A recent large review reported a 32% prevalence of any CI and a 25% prevalence of mild CI (MCI) in patients with COPD (41). More recently, a 39.4% prevalence of CI was reported in clinically stable patients (42), and a 41.5% (43) and 56.7% (13) prevalence in patients referred to PR. In contrast, the prevalence of CI among non-COPD controls in the latter study was 13.3%. In another study in a PR context, 9.5% of patients with COPD scored below the 5th percentile of a normal reference group on the MoCA, and only 38.1% of patients scored higher than the median of the reference group (44).

The consequences of CI extend beyond the cognitive domain. CI affects self-management skills, which are especially relevant in patients with chronic diseases. Cognitive functioning is related to the accuracy of recalling severity of fatigue and dyspnea over a two-week period (45) and to inhaler competency (46) in patients with COPD. Impaired prospective memory and planning can lead to decreased treatment and medication adherence (47). The risks of hospitalization and mortality (48) are higher in patients with CI compared to those without. Cognitive functioning is also related to engagement in unhealthy lifestyle behaviors, such as food intake in overweight people (49) and alcohol consumption in problem drinkers (50). The relationship between CI and health-related quality of life remains unclear: in some studies the two were significantly negatively related (42, 51, 52) but not in others (43, 53).

Cognitive stress susceptibility is already heightened by chronic disease (54), and CI and cerebral abnormalities might further amplify these effects: executive functioning is related to cognitive stress reactivity (55) and perception (56), and the prefrontal cortex and hippocampus are smaller in patients with COPD compared to healthy controls (57-59). These are the two main areas involved in the regulation of the hypothalamic-pituitary-adrenal (HPA) axis, which is activated in response to stress (60, 61). Moreover, exposure to cortisol, which is the end-product of HPA axis activation, contributes to shrinkage of these two areas (62-64), thereby creating a vicious cycle of progressively poorer stress regulation.

Potential etiological factors

Many typical or common factors associated with COPD are independently related to poorer cognitive functioning. All of these likely contribute to CI in COPD, depending on the extent to which they affect any given patient. Disease-specific factors include inflammation (65, 66), exacerbations (51, 67, 68), hypoxemia and hypercapnia (69, 70). Obstructive sleep apnea (71, 72), chronic heart failure (41)

and depression (73) are common comorbidities of COPD. In addition, modifiable lifestyle factors exhibited by many patients with COPD, such as a history of smoking (74), physical inactivity (75-77) and a low-quality diet (78) play a role. Chapter 4 of this dissertation reviews the initial knowledge base around the specific cognitive domains which are predominantly affected in COPD, the prevalence and pathophysiology of CI in COPD and the impact of CI on health, self-management and daily life outcomes.

Metabolic abnormalities, such as MetS and sarcopenia, are more common in COPD compared to non-COPD controls (8, 9), and both are independently related to poorer cognitive performance (79-83). It is still unknown, however, whether MetS and sarcopenia amplify the detrimental impact of COPD on cognitive performance. If MetS and sarcopenia are related to CI in COPD, they could constitute prognostic and potential screening factors for the development of CI and/or interventional targets to prevent or counteract its development. Therefore, Chapter 5 investigates in patients with COPD referred for PR whether cognitive performance is poorer in patients with MetS or sarcopenia compared to those without.

Treating cognitive impairment in COPD

The large impact of CI on the disease management, health outcomes, lifestyle behaviors and cognitive stress susceptibility of patients with COPD emphasizes the importance to treat CI. Cognitive performance is trainable: the brain is plastic (84, 85). Cognitive performance can therefore be improved through repeated practice. One earlier study investigated the effects of cognitive training in patients with COPD, which did not find improved cognitive performance (86). However, this intervention had a relatively low training load and was aimed at improving attention and logical-deductive thinking. In contrast, WM training (WMT) would be especially promising in COPD, because WM is the principal cognitive domain underlying both general cognitive performance (87) and top-down behavioral regulation.

The connection between WM and general cognitive performance implies that the likelihood of training-induced cognitive improvement 'spilling over' into other cognitive domains is largest when WM is trained, as opposed to other cognitive domains. This 'spill-over' is known in the neuropsychological literature as 'transfer' (88). Most cognitive or WM training interventions are aimed at children or adolescents, because their brains are more plastic than those of the elderly (89).

Studies that specifically investigate WMT in healthy elderly populations yield mixed results (90-92), but WMT has never been administered to patients with COPD yet.

The connection between WM and top-down behavioral control is explained by dual-process theories of cognitive functioning (93-95). These postulate the existence of two cognitive processing systems: a fast system and a slower one (95, 96). The fast system is responsible for executing relatively easy, well-known and/or highly automated cognitive processes; the slow system for more deliberate, controlled and conscious execution of harder cognitive tasks (96). WM underlies the latter system (97), which is responsible for top-down behavioral control. Strengthening it would make it easier to execute controlled responses compared to less opportune automatic ones. Several studies have confirmed that cognitive training can decrease engagement in unhealthy lifestyle behaviors, such as overeating in obese people (49) and consuming alcohol in problem drinkers (50), but the effects of cognitive training or WMT on adherence to healthy lifestyle behaviors such as a healthy diet or physical activity (PA) have remained under-Investigated. This is relevant in COPD because a sedentary lifestyle is common in advanced stages of COPD (98-100), as is a poor dietary quality. In 564 patients referred for PR, protein intake deviated from the recommended daily intake in 30% of patients, carbohydrate intake in 26% and dietary fat intake in almost one third (101). Intake of many micronutrients, such as iron, sodium, zinc, niacin, folic acid (102), vitamin B6, B9 and B12, β-carotene (103), vitamins A, C, D (101) and E (101, 103) was low.

Chapter 6 therefore presents the results of the randomized, placebo-controlled Cogtrain trial, investigating whether a 12-week home-based WMT program followed by a 12-week maintenance program could establish and maintain improvement in cognitive performance, physical capacity and activity, dietary quality, cognitive stress susceptibility and perception, recall of prespecified healthy lifestyle goals, healthy lifestyle motivation and psychological wellbeing in patients with COPD.

The results of the current thesis will be discussed and placed in a broader context in Chapter 7, with a particular focus on cognitive functioning in COPD and on the potential efficacy of WMT and other promising interventions to improve cognitive functioning and adherence to a healthy lifestyle in patients with COPD.

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Chapter 2

Clinical outcome and cost-effectiveness of a 1-year nutritional intervention programme in COPD patients with low muscle mass: the randomized controlled NUTRAIN trial

Martijn van Beers
Maureen P. M. H. Rutten-van Mölken
Coby van de Bool
Melinde Boland
Stef P. J. Kremers
Frits M. E. Franssen
Ardy van Helvoort
Harry R. Gosker
Emiel F. Wouters
Annemie M. W. J. Schols

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Abstract

Background and aims: The efficacy of nutritional intervention to enhance short- and long-term outcomes of pulmonary rehabilitation in COPD is still unclear, hence this paper aims to investigate the clinical outcome and cost-effectiveness of a 12-month nutritional intervention strategy in muscle-wasted COPD patients.

Methods: Prior to a 4-month pulmonary rehabilitation programme, 81 muscle-wasted COPD patients (51% males, aged 62.5±0.9 years) with moderate airflow obstruction (FEV_1 55.1±2.2% predicted) and impaired exercise capacity (W_{max} 63.5±2.4% predicted) were randomized to 3 portions of nutritional supplementation per day (enriched with leucine, vitamin D and polyunsaturated fatty acids) [NUTRITION] or PLACEBO (phase 1). In the unblinded 8-month maintenance phase (phase 2), both groups received structured feedback on their physical activity level assessed by accelerometry. NUTRITION additionally received 1 portion of supplemental nutrition per day and motivational interviewing-based nutritional counselling. A 3-month follow-up (phase 3) was included.

Results: After 12 months, physical capacity measured by quadriceps muscle strength and cycle endurance time were not different, but physical activity was higher in NUTRITION than in PLACEBO (Δ 1030 steps/day, p=0.025). Plasma levels of the enriched nutrients (p<0.001) were higher in NUTRITION than PLACEBO. Trends towards weight gain in NUTRITION and weight loss in PLACEBO led to a significant between-group difference after 12 months (Δ 1.54 kg, p=0.041). The HADS anxiety and depression scores improved in NUTRITION only (Δ -1.92 points, p=0.037). Generic quality of life (EQ-5D) was decreased in PLACEBO but not in NUTRITION (between-group difference after 15 months 0.072 points, p=0.009). Overall motivation towards exercising and healthy eating was high and did not change significantly after 12 months; only amotivation towards healthy eating yielded a significant between-group difference (Δ 1.022 points, p=0.015). The cost per quality-adjusted life-year after 15 months was €16,750.

Conclusions: Nutritional intervention in muscle-wasted patients with moderate COPD does not enhance long-term outcome of exercise training on physical capacity but ameliorates plasma levels of the supplemented nutrients, total body weight, physical activity and generic health status, at an acceptable increase of costs for patients with high disease burden.

Introduction

Extra-pulmonary pathology enhances disease burden in patients with chronic obstructive pulmonary disease (COPD) (1). Decreased muscle mass is associated with increased prevalence of osteoporosis, lower muscle strength and exercise performance, and increased mortality risk (2). Furthermore, COPD is characterized by impaired muscle oxidative metabolism, which cannot simply be explained by disuse alone (3, 4) and may predominate in patients with low muscle mass (5).

Exercise training is a cornerstone of pulmonary rehabilitation (PR) (6), and improves lower limb muscle strength, exercise performance, and in some studies also daily physical activity level (7, 8). Protein and specific nutrient supplementation could potentiate the effects of PR or represent an alternative to exercise training in severely deconditioned patients. In contrast to other nutrients including creatine and nitrate (9), to date only polyunsaturated fatty acids (PUFA) (10) and vitamin D (11) have been effective as single-nutrient add-on treatment in COPD by enhancing inspiratory muscle strength (11) and maximal oxygen uptake (10, 11) during PR which could be *via* immune modulation and/or boosting oxidative metabolism. Multimodal nutritional interventions are interesting to explore because the regulation of muscle mass and metabolism is controlled by multiple tightly intertwined pathways (12). In the NUTRAIN trial (13), we developed a multimodal stepwise nutritional intervention approach including high-quality protein enriched with leucine, vitamin D, and omega-3 PUFA, based on evidence regarding the mode of action of these nutrients on skeletal muscle maintenance, combined with reported deficiencies in COPD. The nutritional supplementation was supplemented by nutritional counselling. This approach was investigated in COPD patients with low muscle mass as a susceptible group for accelerated functional decline (14). The results of the first phase, which took place during PR, have been reported earlier (13). During this phase nutritional supplementation improved nutritional status but did not enhance lower limb muscle strength or muscle mass regain. A remarkable between-group difference was shown in physical activity level, largely due to a decline in the PLACEBO group only, whereas the NUTRITION group remained stable, indicating that this nutritional strategy might be effective to attenuate the decline in physical activity typically observed in patients with COPD (15). Exercise-induced muscle fatigue is a commonly reported symptom in COPD (16), and nutritional modulation thereof or nutritional effects beyond the muscle (i.e., the brain or cardiovascular system) (17, 18) might explain this observation. Accordingly, Calder *et al*. (19) showed in a 3-month randomized controlled trial that supplementation with high-quality protein enriched with omega-3 PUFA and

vitamin D, reduced walking exercise-induced fatigue (measured using the Borg scale) in COPD patients with low muscle mass.

We hypothesized that improved nutritional status and positive effects on daily physical activity level might also enhance the long-term efficacy of the intervention with quadriceps muscle strength (QMS) as primary outcome. The current paper aims to investigate the clinical outcome of the overall nutritional management strategy of the NUTRAIN trial, including phase 1, the 8-month maintenance phase after completion of PR (phase 2) and the 3-month follow-up (phase 3). Furthermore, the cost-effectiveness of the intervention after 15 months is explored.

Methods

Study design

The trial was integrated in the outpatient PR program of 7 hospitals in The Netherlands (Sint Anna hospital in Geldrop, Maxima Medical Centre in Veldhoven [until March 2013], Laurentius hospital in Roermond, Sint Jans Gasthuis hospital in Weert, Elkerliek hospital in Helmond, Maastricht University Medical Centre and Catharina hospital in Eindhoven), supervised by CIRO, a center of expertise for patients with chronic organ failure in Horn. Participants were recruited during the assessment period at CIRO when eligible for outpatient PR at one of the hospitals. Patients with severe COPD referred for inpatient PR at CIRO were not included. Every participant underwent an interview with a chest physician at admission; the study physician checked eligibility of potential participants during this visit and asked participants whether they could be contacted by the researcher. The study was registered at clinicaltrials.gov (NCT01344135) and the medical ethics committee of Maastricht University Medical Centre granted ethical approval (NL34927068.10/MEC 11-3-004). All participants provided written informed consent.

The intervention was divided into a 4-month nutritional intervention (phase 1) and an 8-month maintenance phase (phase 2). In short, in the double-blind controlled intervention phase 1, 81 patients were randomized to the PLACEBO (n=39) or NUTRITION group (n=42). Both groups underwent a supervised center-based exercise training program and were advised to consume 3 oral nutritional supplements daily. The NUTRITION product provided protein, carbohydrates, fat and micronutrients, and was enriched with leucine, omega-3 PUFA and vitamin D (Nutricia NV, Zoetermeer, The Netherlands). The PLACEBO product did not

comprise the active components, but consisted of a flavored non-caloric cloudified aqueous solution. For details see Van de Bool *et al.* (13).

In the open-label maintenance phase (phase 2), both groups received feedback on their daily physical activity behavior twice, based on accelerometry. This was done in order to offer both groups a follow-up intervention aimed at maintaining long-term efficacy of the exercise training. In addition, participants in NUTRITION were advised to take 1 oral nutritional supplement per day and received four nutritional counselling sessions. These were provided by trained nurses, and aimed to optimize participants' dietary habits and maximize adherence to a healthy diet and the supplement regime. The counselling was based on self-determination theory (SDT) (20), which assumes that autonomous forms of motivation are essential to achieve lasting behavioral change, and it was operationalized through motivational interviewing (MI) (21). After the 8-month maintenance phase, participants were followed up for three months, without any intervention taking place in either group (phase 3). Figure 1 depicts a flowchart of the study; Figure 2 outlines the study design.

Patients

Patients with COPD (post-bronchodilator $FEV_1/FVC < 0.7$) referred for outpatient PR between September 2011 and April 2014 were eligible for participation if they had low muscle mass, defined as a fat-free mass index (FFMI) below the sex- and age-specific 25th percentile FFMI values (22). Exclusion criteria were age under 18 years old, allergy or intolerance to components of the study product, investigator's uncertainty about patients' willingness or ability to comply with the protocol requirements, inability to stop current supplement use, participation in any other study involving investigational or marketed products concomitantly or less than two weeks prior to entry into the study, pregnancy, or life-threatening diseases.

Outcomes

Quadriceps muscle strength (QMS), assessed by dynamometry (System 4 Pro; Biodex Medical Systems Inc., New York, USA) served as the primary outcome of this study. QMS, body composition measured by dual energy x-ray absorptiometry (DEXA) (Lunar Prodigy system; GE Healthcare, Madison, WI, USA), cycle endurance time (CET) on a cycle ergometer (Carefusion, Houten, The Netherlands) (determined using the constant work rate cycling endurance test at 75% of the peak workload), and fasting plasma levels of vitamin D, eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA) and leucine were measured at baseline (before

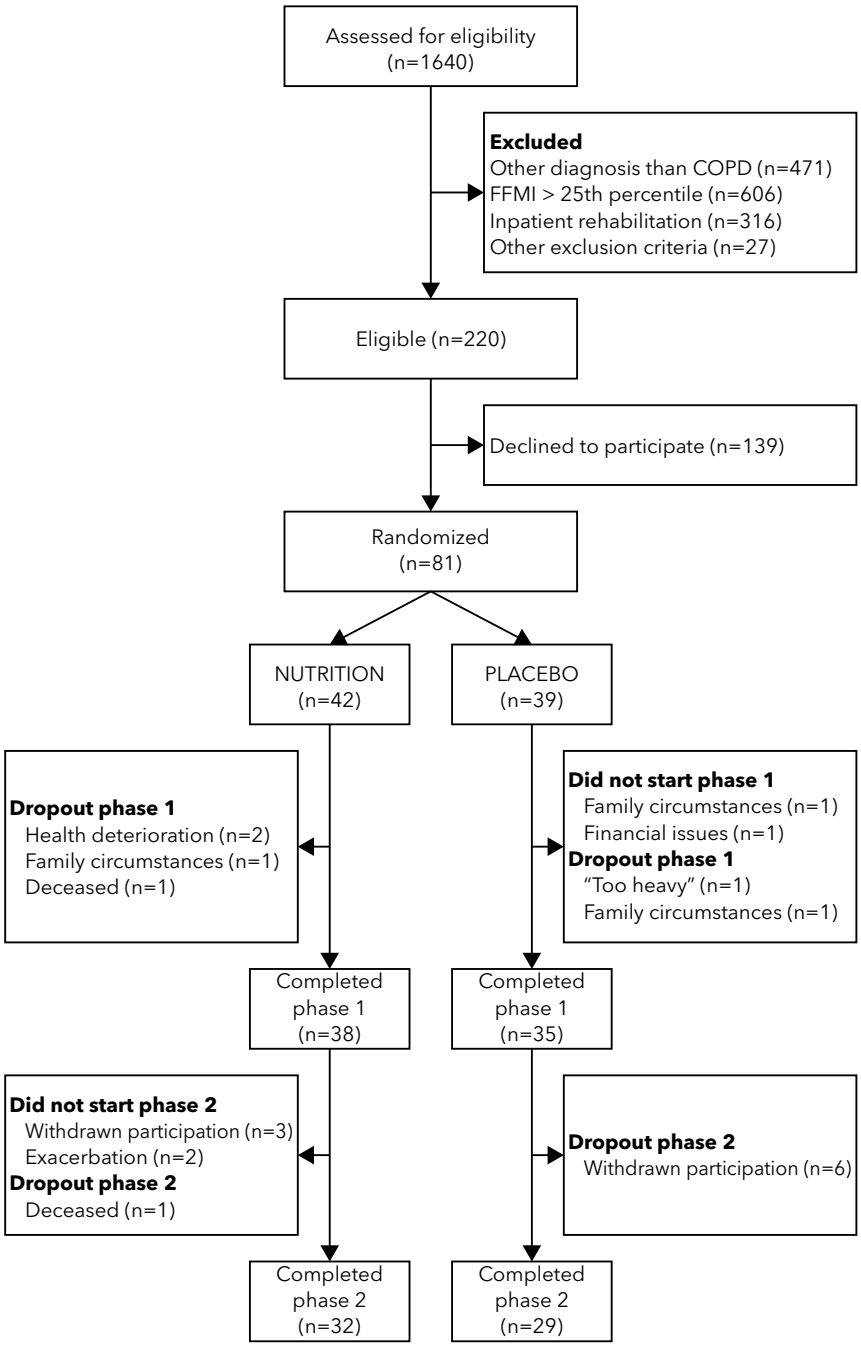

Figure 1

Consort flow chart

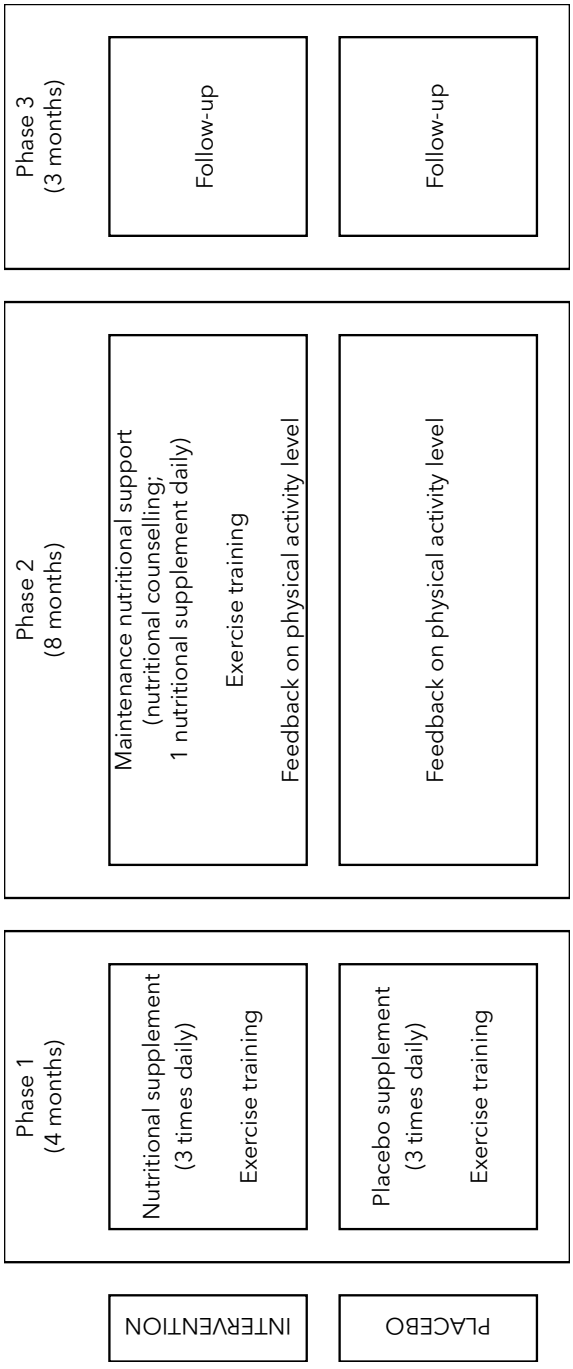

Figure 2

Study design

entering PR), and after phase 1 and 2. Habitual dietary intake of the last month was assessed at these time points by trained dieticians using a validated cross-check dietary history method and calculated using the Dutch Food Composition Database. Mental and physical health status, assessed by the Hospital Anxiety and Depression Scale (HADS) (23), EuroQoL Five-Dimensions Questionnaire (EQ-5D-3L) (24), St George's Respiratory Questionnaire (SGRQ) (25) and physical activity level (PAL) as assessed by daily steps by a tri-axial GT3X Actigraph accelerometer (Health One Technology, Fort Walton Beach, FL, USA) were measured at baseline and after phase 1, 2 and 3. Post-bronchodilator forced expiratory volume in 1 second (FEV_1) and forced vital capacity (FVC) were assessed by standardized equipment (Masterlab®; Jaeger, Würzburg, Germany), in accordance with the latest GOLD guidelines (26). The Dutch value set was used to transform EQ-5D scores into utilities (27). Adopting such a wide range of outcome measures is in line with the recommendations of the joint ATS/ERS task force on outcome measures in COPD to use a multi-outcome approach (28).

Participants' motivational profiles towards exercising and healthy eating were assessed using the Behavioral Regulation in Exercise Questionnaire-2 (BREQ-2) (29) and the Regulation of Eating Behaviors Scale (REBS) (30), respectively, at baseline and after phase 1, 2 and 3. These questionnaires are based on SDT and they provide six subscale scores (see (20) for details). Answers were given on a 5-point Likert scale in both questionnaires. Scores on the BREQ range from 1 (lowest possible motivation) to 5 (highest possible motivation). Scores on the REBS range from 0 (lowest possible motivation) to 10 (highest possible motivation). Internal consistency measured by Cronbach's α was adequate for all scales, except for identified regulation towards exercising (α = 0.319 after phase 2). Consequently, this scale was excluded from subsequent analyses.

Costs

Total costs (not only related to COPD) were calculated from a healthcare and a societal perspective. The healthcare perspective included all costs covered by the healthcare budget. The societal perspective additionally included travel costs and costs of productivity loss due to absence form paid work (absenteeism). Healthcare utilization, travel distance and absenteeism were assessed in a resource use questionnaire after phase 1, 2 and 3.

The intervention costs included the reported number of supervised exercise training sessions and their duration, the number of nutritional supplements used, the number of educational counselling sessions and their duration, the number

of consultations for physical activity level feedback, the number of nutritional counselling sessions and the travel distance to health care providers.

Standard unit costs were determined using Dutch guideline prices (31) and inflated to 2015 values using the general consumer price index (32). The costs of medication were obtained from the Drug Information System of the Dutch National Health Care Institute and included value added tax and pharmacist dispensing fees (33). The productivity costs were estimated using the Friction Cost Approach, which assumes that productivity loss occurs as long as a sick employee is not replaced (the friction period) (34). We used a friction period of 85 days. The unit costs are shown in Supplementary Tables 1 through 3.

Statistical analyses

Statistical analyses were performed using Stata, in accordance with the intention-to-treat principle.

Plasma levels of the supplemented nutrients, body composition, motivational profile and physical function were analyzed using a linear repeated measurement model with correlated error terms and unstructured covariance matrix. The model included treatment, time (i.e., the measurements at 4 and 12 months) and treatment by time interactions. Data from patients who discontinued the trial prematurely were included in the analyses up to the point of drop-out.

Costs were also analyzed in a linear repeated measures model with correlated error terms and unstructured covariance matrix. The dependent variable was total costs in a certain phase, and the explanatory variables were time (4, 12 and 15 months) and the interaction of treatment and time. The results were used to predict the mean costs per treatment group for each phase. Total costs were calculated as the sum of the predicted costs of the rehabilitation phase, maintenance phase and follow-up phase.

To assess differences in health outcomes between the two treatment groups, we also used linear repeated measurement models with correlated errors and unstructured covariance matrix. Explanatory variables were time (4, 12 [and, if applicable, 15] months) and the interaction of treatment and time. We calculated the number of quality-adjusted life-years (QALYs) for each patient as the area under the predicted utility curve, using linear interpolation between two measurements.

The costs per gained QALY were calculated as the difference in total costs between the two groups divided by the difference in QALYs. Uncertainty around this cost-effectiveness ratio was estimated by performing 5000 bootstrap replications.

Power calculation

The power calculation was based on the INTERCOM study assuming a 10% between-group difference in peak torque assuming maintenance of skeletal muscle strength in NUTRITION during follow-up and a standard deviation of 5 Nm in peak torque. Allowing for 25% drop-out yielded a subgroup size of n=60. Patient inclusion was prematurely discontinued because the test product could not be produced within the appropriate quality specifications due to discontinuation of the supply of one of the ingredients, but the sample size was justifiable based on other RCTs published in the meantime (13).

Results

Patients

Baseline characteristics did not differ between the groups, except for a higher peak workload in NUTRITION. The study population consisted of 51% males, aged 62.5±0.9 years, and was characterized by low diffusion capacity (DLCO 49.4±1.7%), moderate airflow limitation (FEV_1 55.1±2.2% predicted), normal to low BMI (22.7±0.3 kg/m^2), impaired exercise capacity (W_{max} 63.5±2.4% predicted), and low FFMI (15.8±1.6 kg/m^2) (see Table 1).

Physical functioning

No between-group difference was observed in improved physical capacity (QMS and CET) (see Table 2). When QMS was normalized for appendicular lean mass or fat-free mass, the between-group difference was not significant either (data not shown). Physical activity level was significantly lower compared to baseline in PLACEBO whereas it remained stable in NUTRITION. This led to a significant between-group difference on number of steps per day (p=0.025) (see Figure 3). Activity intensity did not differ significantly over time or between the groups: in both groups across all time points, patients spent around 70% in sedentary physical activity (PA), 23% in lifestyle PA, 6% in light PA and 1% in moderate-to-vigorous PA.

Table 1

Baseline characteristics

	NUTRITION	**PLACEBO**
General		
Gender (% male)	42.9%	59.0%
Age (years)	62.8±1.3	62.2±1.3
Current smokers (%)	19.0%	31.6%
Low SES (no or only primary education (%)	5.6%	13.3%
Employed (%)	33.3%	19.4%
Number of exacerbations in the last year	1.1±0.2	1.4±0.3
Lung function		
FEV_1 (% predicted)	57.0±3.3	53.0±2.8
FVC (% predicted)	102.8±2.9	100.6±2.7
FEV_1/FVC (%)	44.4±2.0	41.6±1.8
Functional residual capacity (% predicted)	139.1±4.3	146.7±5.9
Residual volume (% predicted)	143.4±6.3	153.1±8.5
DLCO (% predicted)	51.4±2.2	47.1±2.5
Physical function		
Quadriceps muscle strength (Nm)	121.5±6.4	118.0±6.6
Cycle endurance time (s)	319.0±35.2	231.5±12.0
Peak workload (W_{max})	84.6±5.2	72.5±3.8
Peak workload (% predicted)	69.5±3.3**	57.0±3.4
Physical activity level (steps per day)	4716.7±327.2	4516.6±379.3
Dietary intake		
Energy (kcal)	2426.0±168.0	2442.8±174.2
Protein (g)	91.1±5.5	89.9±5.5
Carbohydrates (g)	263.1±19.9	266.8±17.5
Fat (g)	103.1±9.8	105.4±12.3
Polyunsaturated fatty acids (g)	20.2±2.0	21.5±2.7
Cholesterol (mg)	251.5±25.2	239.1±25.2
Dietary fiber (g)	21.9±1.3	21.7±1.6

Table 1 (continued)

	NUTRITION	**PLACEBO**
Calcium (mg)	1083.5±96.1	977.3±67.5
Vitamin A (µg)	1241.4±96.5	1192.5±145.8
Vitamin C (mg)	84.1±6.1	85.9±6.9
Vitamin D (µg)	5.3±0.4	5.1±0.6
Vitamin E (mg)	14.6±1.3	13.9±1.2
Supplemented plasma nutrient levels		
Leucine (µmol/l)	147.7±3.6	153.5±3.5
Vitamin D (nmol/l)	54.0±4.5	45.3±3.1
Eicosapentaenoic acid (mg/l)	1.1±0.1	1.2±0.1
Docosahexaenoic acid (mg/l)	2.9±0.2	3.2±0.2
Body composition		
Total weight (kg)	64.3±1.6	65.0±1.7
Bone mineral content (g)	2331.3±73.0	2414.7±82.3
Appendicular skeletal muscle mass (kg)	17.4±0.6	18.4±0.6
Fat mass (kg)	20.0±1.0	19.0±1.3
Lean mass (kg)	42.0±1.3	43.6±1.2
Body mass index (kg/m^2)	22.9±0.4	22.6±0.5
Fat-free mass index (kg/m^2)	15.7±0.3	15.9±0.2
Patient-reported outcomes		
EuroQoL 5-dimensions questionnaire	0.8±0.0	0.8±0.0
St George's Respiratory Questionnaire	49.9±2.4	50.1±2.6
Hospital Anxiety and Depression Scale - total	10.9±1.2	10.2±1.1

*All data given as mean ± standard error, unless noted otherwise. DLCO: diffusion capacity of the lung for carbon monoxide; FEV_1: forced expiratory volume in 1 second; FVC: forced vital capacity; Nm: Newtonmeter; SES: socio-economic status. ** p<0.01.*

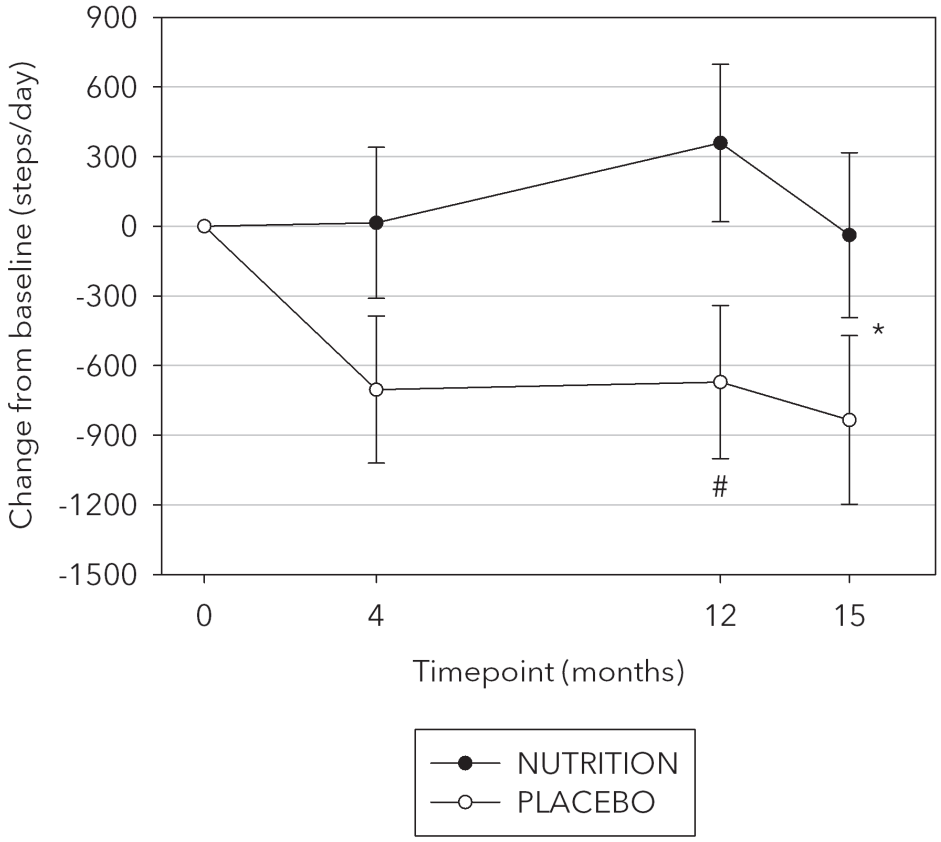

Figure 3

Development of physical activity level as change from baseline. # within-group p*<0.05 (compared to baseline); * between-group* p*<0.05.*

The change in physical activity level from baseline to T12 correlated significantly with the change in appendicular skeletal muscle mass index (ASMI) (r=0.371, p=0.022) but not that in total body weight (r=0.088, n.s.) in the entire study population.

Dietary intake and plasma nutrient status

Overall dietary habits represented a typical Western diet and no significant within- or between-group changes were identified throughout the trial on any macronutrient or micronutrient, except for cholesterol intake (see Supplementary Table 4). Cholesterol intake was significantly higher in PLACEBO after 12 months

Table 2

Within- and between-group differences in plasma nutrient status, physical function, body composition and patient-reported outcomes, after 12 months

	Within-group				**Between-group**	
	NUTRITION		**PLACEBO**			
Measure	**adj. *M* (*SE*)**	***Z***	**adj. *M* (*SE*)**	***Z***	**adj. *M* (*SE*)**	***Z***
Physical function						
QMS (Nm)	10.35±3.51	2.95**	10.05±3.46	2.90**	0.30±4.92	0.06
CET (s)	107.1±62.9	1.70*	200.3±64.5	3.11**	-93.2±89.8	1.04
PAL (steps/day)	358.8±339.9	1.06	-671.3±330.3	-2.03*	1030.1±459.8	2.24*
Supplemented plasma nutrient levels						
Leucine (µmol/l)	10.41±5.57	1.87	-6.08±5.80	-1.05	16.49±8.01	2.06*
Vitamin D (nmol/l)	15.10±2.69	5.61***	1.25±2.77	0.45	13.85±3.84	3.60***
EPA (mg/l)	5.42±1.66	3.27**	-3.34±1.64	-2.04*	8.76±1.95	4.49***
DHA (mg/l)	7.26±2.69	2.70**	-4.69±2.67	-1.76	11.97±3.47	3.45**
Body composition						
Total weight (kg)	0.64±0.53	1.21	-0.90±0.54	-1.67	1.54±0.76	2.04*
BMC (g)	-9.96±13.81	-0.72	-22.21±14.12	-1.57	12.26±19.73	0.62
ASM (kg)	0.17±0.21	0.83	-0.22±0.21	-1.02	0.39±0.29	1.32
Fat mass (kg)	0.86±0.50	1.71	-0.47±0.51	-0.91	1.33±0.72	1.86

Table 2 (continued)

	Within-group				Between-group	
	NUTRITION		PLACEBO			
Measure	**adj. *M* (*SE*)**	***Z***	**adj. *M* (*SE*)**	***Z***	**adj. *M* (*SE*)**	***Z***
Patient-reported outcomes						
EQ-5D	-0.003±0.03	-0.10	-0.07±0.03	-2.63**	0.07±0.04	1.86
SGRQ	1.43±1.89	0.75	-0.71±1.97	-0.04	2.14±2.73	0.78
HADS - total	-1.92±0.92	-2.09*	-1.50±0.97	-1.54	-0.42±1.30	-0.32

*Values shown as change from baseline. ASM: appendicular skeletal muscle mass; BMC: bone mineral content; CET: cycle endurance time; DHA: docosahexaenoic acid; EPA: eicosapentaenoic acid; EQ-5D: EuroQoL 5-dimensions questionnaire; HADS: Hospital Anxiety and Depression Scale; Nm: Newtonmeter; PAL: physical activity level; QMS: quadriceps muscle strength; SGRQ: St George's Respiratory Questionnaire. * p<0.05; ** p<0.01; *** p<0.001.*

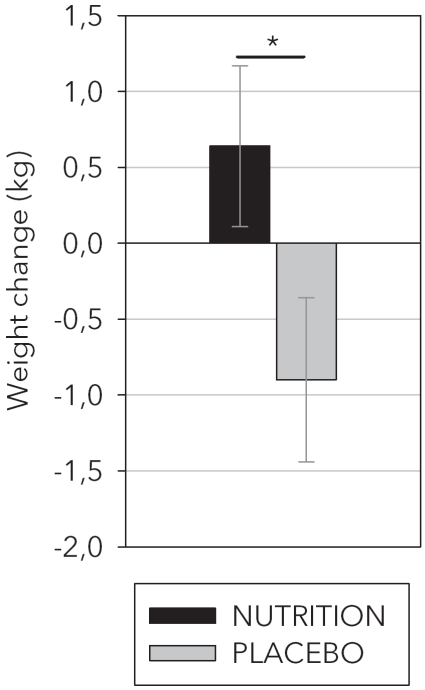

Figure 4

*Change in total body weight from baseline to T12. * between-group* p<*0.05.*

compared to baseline (p=0.001), leading to a significant between-group difference (p=0.003). At baseline, 31.2% of participants had vitamin D insufficiency, whereas 57.5% had vitamin D deficiency.

Plasma vitamin D, EPA and DHA levels were significantly increased compared to baseline in NUTRITION. EPA levels were significantly decreased compared to baseline in PLACEBO. Leucine, vitamin D, EPA and DHA levels significantly differed between groups (see Table 2).

Body composition

Total body weight, muscle mass and fat mass tended to decrease within PLACEBO and tended to increase within NUTRITION from baseline to the end of phase 2. This resulted in a significant between-group difference in total body weight change, in favor of NUTRITION (Δ1.54±0.76 kg, p=0.041) (see Table 2 and Figure 4).

Table 3

Within- and between-group differences in physical activity level and patient-reported outcomes, after 15 months.

	Within-group				Between-group	
	NUTRITION		PLACEBO			
Measure	**adj. *M* (*SE*)**	***Z***	**adj. *M* (*SE*)**	***Z***	**adj. *M* (*SE*)**	***Z***
PAL (steps per day)	-38.1±355.5	-0.11	-834.2±362.8	-2.30*	796.1±496.9	1.60
EQ-5D	0.012±0.02	0.49	-0.060±0.02	-2.53*	0.072±0.03	2.12*
SGRQ	0.16±2.11	0.08	2.72±2.19	1.24	-2.56±3.00	-0.86
HADS - total	-0.85±0.97	-0.87	-1.74±0.98	-1.78	0.89±1.38	0.65

*Values shown as change from baseline. EQ-5D: EuroQoL 5-dimensions questionnaire; HADS: Hospital Anxiety and Depression Scale; PAL: physical activity level; SGRQ: St George's Respiratory Questionnaire. * p<0.05.*

Patient-reported outcomes

Total HADS score significantly improved in NUTRITION (p=0.037). In PLACEBO, the EQ-5D score decreased significantly (p=0.009) (see Table 2). The SGRQ did not differ significantly within or between groups. After phase 3, EQ-5D utility was still significantly decreased compared to baseline in PLACEBO (p=0.011), whereas the between-group difference was also significant in favor of NUTRITION (p=0.034) (see Table 3).

Interestingly, the change in EQ-5D scores from baseline to T12 correlated significantly with the change in total body weight (r=0.406, p=0.008) and ASMI (r=0.456, p=0.003) in the entire study population.

Motivational profile

Motivation towards both exercising and healthy eating was already high before the counselling sessions started. The mean scores for intrinsic and identified motivation towards exercising before the counselling started were 4.14 and 4.03 out of 5, respectively. These figures were 7.69 and 8.42 out of 10 for intrinsic and identified motivation towards healthy eating. In NUTRITION, amotivation towards exercising decreased (p=0.015) while in PLACEBO identified motivation towards healthy eating decreased (p=0.019). Only amotivation towards healthy eating differed significantly between groups (p=0.015) (see Table 4).

Intervention costs

Intervention costs are presented in Supplementary Table 1. From a healthcare perspective, the mean intervention costs of the total intervention were €2,233 per patient in NUTRITION and €1,372 in PLACEBO. From a societal perspective, these costs were €2,265 and €1,404, respectively. The between-group difference is mainly due to the costs of the nutritional supplements. Supervised exercise training was the main driver of the intervention costs in both groups.

Total costs and cost-effectiveness

Tables 5 and 6 show the cost-effectiveness analysis after phase 2 and 3. The differences in various categories of healthcare utilization over 12 and 15 months are presented in Supplementary Tables 2 and 3. After phase 2, the costs in NUTRITION were estimated to be €1,529 (certainty 87%) higher than in PLACEBO from the healthcare perspective and €2,829 (certainty 98%) higher from the societal perspective. After phase 3, costs in NUTRITION were €670 (certainty 64%)

Table 4

Within- and between-group differences in motivational profile, after 12 months

	Within-group				Between-group	
	NUTRITION		PLACEBO			
Measure	**adj. *M* (*SE*)**	***Z***	**adj. *M* (*SE*)**	***Z***	**adj. *M* (SE)**	***Z***
Exercise						
Intrinsic	0.069±0.11	0.60	0.011±0.12	0.09	0.058±0.16	0.36
Introjected	-0.183±0.16	-1.12	0.212±0.17	1.25	-0.396±0.23	-1.72
External	0.006±0.10	0.06	-0.006±0.10	-0.06	0.012±0.13	0.09
Amotivation	-0.232±0.10	-2.43*	-0.011±0.10	-0.17	-0.215±0.13	-1.71
Healthy eating						
Intrinsic	-0.094±0.26	-0.36	0.060±0.27	0.22	-0.154±0.37	-0.42
Integrated	0.040±0.29	0.14	-0.230±0.31	-0.76	0.271±0.40	0.67
Identified	-0.028±0.24	-0.12	-0.577±0.24	-2.35*	0.549±0.34	1.60
Introjected	-0.437±0.29	-1.50	-0.644±0.30	-0.21	-0.373±0.41	-0.91
External	-0.297±0.38	-0.78	-0.122±0.39	-0.31	-0.175±0.53	-0.33
Amotivation	-0.492±0.30	-1.44	0.593±0.31	1.92	-1.022±0.42	-2.43*

*Values shown as change from baseline. * p<0.05.*

Table 5

Cost-effectiveness and cost-utility: 12-month time horizon

	NUTRITION	**PLACEBO**	**Difference (95% UI)**
Costs (€)			
Healthcare perspective	8,094	6,565	1,529 (-1,007 - 4,343)
Societal perspective	9,404	6,575	2,829 (100 - 5,802)
Effects			
QALYs	0.66	0.64	0.025 (-0.02 - 0.07)
PAL (steps/day)	4,960	3,940	1,020 (17 - 1,990)
Percentage of patients with +4 units improvement in SGRQ	0.36	0.43	-0.07 (-0.38 - 0.22)
ICER (€)	*HCP*	*SCP*	
Costs / QALY gained	61,160	113,160	
Costs / 1000 additional steps	1,499	2,774	
Costs / additional patient with +4 units improvement in SGRQ	dominated	dominated	

** p<0.05. HCP: healthcare perspective; PAL: physical activity level; QALY: quality-adjusted life year; SCP: societal perspective; SGRQ: St George's Respiratory Questionnaire; UI: uncertainty interval.*

higher from the healthcare perspective and €2,401 (certainty 92%) higher from the societal perspective.

Both from a healthcare and societal perspective, the point-estimates of costs pointed towards higher costs in NUTRITION and a higher physical activity level in NUTRITION after phase 2, and a higher number of QALYs in NUTRITION after phase 3. The probability that the nutritional intervention was cost-effective at a willingness-to-pay of €20,000 and €80,000 per QALY was 27% and 59% after phase 2 and 55% and 82% after phase 3 (data not shown).

Discussion

This paper investigated the clinical benefits and cost-efficacy of a 12-month multimodal, stepwise nutritional intervention strategy in patients with moderate

Table 6

Cost-effectiveness and cost-utility: 15-month time horizon

	NUTRITION	**PLACEBO**	**Difference (95% UI)**
Costs (€)			
Healthcare perspective	9,548	8,878	670 (-2,468 - 4,001)
Societal perspective	11,324	8,923	2,401 (-854 - 5,824)
Effects			
QALYs	0.86	0.82	0.04 (-0.01 - 0.10)
PAL (steps/day)	4,576	3,780	814 (-335 - 1,838)
Percentage of patients with +4 units improvement in SGRQ	0.35	0.23	0.12 (-0.16 - 0.39)
ICER (€)	*HCP*	*SCP*	
Costs / QALY gained	16,750	60,025	
Costs / 1000 additional steps	823	2,950	
Costs / additional patient with +4 units improvement in SGRQ	5,583	20,008	

** p<0.05. HCP: healthcare perspective; PAL: physical activity level; QALY: quality-adjusted life year; SCP: societal perspective; SGRQ: St George's Respiratory Questionnaire; UI: uncertainty interval.*

COPD and low muscle mass. Physical capacity, as primary outcome, was improved in both groups after 12 months, but NUTRITION took 1,030 additional steps per day compared to PLACEBO. This difference exceeds the minimal important difference to reduce risk of hospital admission (35), and it cannot be explained by greater energy substrate availability, as total macronutrient intake was not significantly different between the groups at T12 (data not shown). This indicates that nutrient-specific mechanisms could explain the dissociation between changes in QMS and physical activity via various synergistic pathways including immune modulation (PUFA, vitamin D) (36, 37), enhancing muscle oxidative metabolism (PUFA) (38) and modifying muscle maintenance regulation (PUFA, leucine) (39, 40).

Plasma levels of the supplemented nutrients after 12 months were indeed significantly higher in NUTRITION compared to both baseline and PLACEBO, indicating that the phased intervention strategy was feasible and overall compliance was good.

Trends towards weight gain in NUTRITION and weight loss in PLACEBO after 12 months led to a significant between-group difference in total body weight. A tendency to lose weight in PLACEBO was also found after 12 months in a trial focusing on protein-calorie supplementation by Weekes *et al.* (41). Changes in muscle and fat mass parallelled total weight change but were not significant, possibly due to lack of power. Remarkably, in contrast to weight change, the subtle change in muscle mass correlated significantly with the change in PA.

Previous studies in weight-losing and muscle-wasted patients with advanced COPD showed positive short-term (1-4 months) effects of protein-calorie supplementation as adjunct to exercise training on physical capacity and muscle mass (42-44), but limited evidence is available in less advanced airflow obstruction. The INTERCOM trial, which investigated a combined nutritional and exercise intervention in the subgroup of patients with low muscle mass and reduced cycle exercise capacity, also showed positive effects on muscle mass and physical capacity in less advanced COPD patients with low muscle mass (14). However, it could not disentangle the relative contributions of the exercise and nutritional interventions to physical performance, because the muscle-wasted control group only received usual care. In the 20-month maintenance phase of the INTERCOM trial, physical capacity remained improved in the subgroup of treated muscle-wasted patients, but 6-minute walking distance declined below baseline in those receiving usual care (14). Whereas the nutritional intervention strategy had no short- or long-term added value on physical capacity in the current trial (13), there were sustained positive effects on body weight, plasma nutrient levels and physical activity and a trend towards improved mental health, which could explain the difference in generic health status after follow-up.

Both EQ-5D and physical activity levels remained stable in NUTRITION and declined in PLACEBO after 12 and 15 months. These parallel changes could mean that generic health status is influenced by daily physical activity level *via* modulation of physiological and / or mental health.

A qualitative study in a random sample of 22 NUTRAIN participants after phase 2 identified perceived competence and autonomous motivation as determinants of a physically active lifestyle (45). The limited between-group motivational differences could be partly explained by high levels of both intrinsic and extrinsic motivation and low levels of amotivation already apparent before counselling. Admission to PR already requires being motivated and participating in an extensive study such as this one even more so. Even so, slight changes in motivational profile may indicate some effect of the nutritional counselling.

The incremental cost-effectiveness ratio (ICER) of €61,160 after phase 2 decreased to €16,750 after phase 3, because of a higher gain in QALYs and lower difference in costs after phase 3. Whether an intervention is cost-effective or not depends on the threshold value of the willingness-to-pay for a QALY. In The Netherlands this threshold depends on disease burden (defined as proportional shortfall) (46). A higher threshold applies for conditions with a higher disease burden. There are three categories, defining a low burden (proportional shortfall of 0.1-0.4 QALYs), medium (0.41-0.7) and high burden of disease (0.71-1), corresponding of threshold values of €20,000, €50,000 and €80,000 per QALY, respectively (47). Hence, an ICER below €20,000 (after phase 3) is generally considered to be cost-effective. With an ICER of around €60,000 after phase 2, the current nutritional intervention would be cost-effective for COPD patients with a disease burden of at least 0.7 QALYs. However, this estimation is associated with high uncertainty illustrated by a small proportion of bootstrap replications below a threshold value of €80,000 after phase 2.

A weakness of the current study includes the unblinding after PR, which was done because it was considered unethical to continue placebo supplementation during the maintenance phase. Secondly, as already mentioned, the current study included quite a small number of patients, in line with many other comparable studies. Generalizability of the study is limited by the fact that only patients referred for PR were included. Thirdly, not achieving the sample size specified beforehand could limit our ability to detect significant results. Finally, the counselling sessions were given by nurses who lacked detailed knowledge on the domains to be improved. More detailed and tailored advice could improve adherence to a healthy lifestyle and increase health gains.

Conclusion

A stepwise multimodal nutritional intervention strategy, consisting of targeted nutritional supplementation and nutritional counselling, in muscle-wasted patients with moderate COPD does not enhance long-term outcome of exercise training on physical capacity but ameliorates plasma levels of the supplemented nutrients, body weight, physical activity and generic health status. This intervention increases total health care costs to a degree that might be considered acceptable for patients with a high disease burden.

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Appendix

Supplementary Table 1

Intervention costs (in euros, 2015)

				NUTRITION			PLACEBO		
	Unit cost	**Source**	**Mean cost (all patients)**	**Any use (%)**	**Mean use**	**Mean cost (users)**	**Any use (%)**	**Mean use**	**Mean cost (users)**
Phase 1									
Supervised exercise training sessions	33	a	1,235±24	100	36	1,197±42	95	39	1,279±17
Reference priced product, # supplements	2.63	b	293±39	100	215	565±43	-	-	-
Nutrition placebo, # supplements	-	-		-	-	-	95	272	-
Education, training sessions	8.93	a	125		14	125	100	14	125
Travel expenses, public transport/car, per km	0.19	a	31±1	100	160	30±1	100	171	32±0.5
Phase 2									
Feedback on physical activity, consultations	33	a	37±3	69	1.2	39±4	59	1.1	34±5
Nutritional counselling, consultations	17	a		55	3.5	59±2	-	-	-
Reference priced product, # supplements	2.63	b		50	208	548±35	-	-	-

Supplementary Table 1 (continued)

				NUTRITION			PLACEBO		
	Unit cost	**Source**	**Mean cost (all patients)**	**Any use (%)**	**Mean use**	**Mean cost (users)**	**Any use (%)**	**Mean use**	**Mean cost (users)**
Travel expenses, public transport/car, per km	0.19	a	0.9c0.1	74	7	1.2±0.2	59	2.3	0.4±0.06
Total costs from health-care perspective			1,818±76			2,233±104			1,372±50
Total costs from societal perspective			1,850±77			2,265±105			1,404±51

Costs are reported in euros and expressed as mean ± standard deviation. Sources of unit costs used in the analysis: (a) Dutch guidelines for pharmacoeconomic research, (b) Z-index.

Supplementary Table 2

Unit costs, data sources, mean unadjusted use of resources and associated costs over 12 months, as reported by the patients (excluding costs related to the intervention program)

			NUTRITION			PLACEBO		
	Unit cost	**Source**	**Any use (%)**	**Mean use**	**Mean cost**	**Any use (%)**	**Mean use**	**Mean cost**
Costs from healthcare perspective								
General practitioner	17-50	a	79	4.60	144±19	74	4.54	138±35
Office consultations	33	a	69	3.00	98±15	67	2.38	79±20
Home visits	50	a	7	0.17	8±5	8	0.44	22±13
Phone contacts	17	a	17	0.33	6±2	21	0.59	10±4
Practice nurse consultations	17	a	17	0.40	7±3	26	0.77	13±4
Specialist, visits	91	a	76	5.40	492±98	72	6.85	623±173
Emergency department, visits	166	a	14	0.52	136±70	13	0.26	66±41
Physiotherapist, visits	33	a	48	21.4	706±151	36	18.9	624±165
Dietician, visits	30	a	38	0.86	26±8	41	0.95	32±10
Podiatrist, visits	34	b	24	1.10	37±12	13	0.58	20±10
Speech therapist, visits	30	a	2	0.05	1±1	5	0.15	5±3
Occupational therapy, visits	33	a	33	0.88	34±12	28	0.44	14±4
Home care, hours	22-78		10	2.66	74±44	15	9.57	305±148
Hospital stay, days			19	2.31	1,541±687	18	0.79	378±161

Supplementary Table 2 (continued)

			NUTRITION			PLACEBO		
	Unit cost	**Source**	**Any use (%)**	**Mean use**	**Mean cost**	**Any use (%)**	**Mean use**	**Mean cost**
No intensive care unit, days	476	a	19	2.03	965±433	18	0.79	378±161
Intensive care unit, days	2,015	a	10	0.29	576±324	0	0	0
Medication								
Drugs for obstructive airway diseases	-	c	86	-	1,085±195	79	-	1,308±324
Drugs for cardiovascular disease	-	c	40	-	171±48	49	-	188±47
Drugs for diabetes	-	c	5	-	31±29	8	-	5±3
Costs from societal perspective								
Travel expenses, public transport/car, per km	0.19	a	83	179	34±7	82	157	30±8
Productivity loss, absenteeism hours	32-38	a	10	27	1,303±666	0	0	0

Costs are reported in euros and expressed as mean ± standard deviation. Sources of unit costs used in the analysis: (a) Dutch guidelines for pharmaco-economic research, (b) Z-index.

Supplementary Table 3

Unit costs, data sources, mean unadjusted use of resources and associated costs over 15 months, as reported by the patients (excluding costs related to the intervention program)

			NUTRITION			PLACEBO		
	Unit cost	**Source**	**Any use (%)**	**Mean use**	**Mean cost**	**Any use (%)**	**Mean use**	**Mean cost**
Costs from healthcare perspective								
General practitioner	17-50	a	81	5.47	170±23	77	5.01	154±38
Office consultations	33	a	71	3.50	116±17	67	2.56	85±20
Home visits	50	a	12	0.21	11±6	10	0.51	26±15
Phone contacts	17	a	17	0.40	7±3	21	0.64	11±5
Practice nurse consultations	17	a	17	0.52	9±4	26	0.77	13±4
Specialist, visits	91	a	81	6.10	555±102	74	7.79	709±182
Emergency department, visits	166	a	21	0.60	154±70	23	0.36	93±42
Physiotherapist, visits	33	a	50	27.6	910±198	51	26.4	870±212
Dietician, visits	30	a	43	1.00	30±8	49	1.26	42±11
Podiatrist, visits	34	b	24	1.21	41±13	13	0.66	22±11
Speech therapist, visits	30	a	2	0.05	1±1	8	0.26	8±4
Occupational therapy, visits	33	a	33	0.88	34±12	28	0.44	14±4
Home care, hours	22-78		12	2.70	76±44	151	10.0	326±161
Hospital stay, days			21	2.66	1,704±725	28	1.64	821±285

Supplementary Table 3 (continued)

			NUTRITION			PLACEBO		
	Unit cost	**Source**	**Any use (%)**	**Mean use**	**Mean cost**	**Any use (%)**	**Mean use**	**Mean cost**
No intensive care unit, days	476	a	21	2.37	1,128±484	28	1.62	769±272
Intensive care unit, days	2,015	a	10	0.29	576±324	3	0.03	52±52
Medication								
Drugs for obstructive airway diseases	-	c	86	-	1,198±203	79	-	1,453±333
Drugs for cardiovascular disease	-	c	40	-	185±53	49	-	220±55
Drugs for diabetes	-	c	5	-	39±37	8	-	6±4
Costs from societal perspective								
Travel expenses, public transport/car, per km	0.19	a	86	216	41±8	82	210	40±9
Productivity loss, absenteeism hours	32-38	a	14	31.9	1,553±673	3	1.08	47±40

Costs are reported in euros and expressed as mean ± standard deviation. Sources of unit costs used in the analysis: (a) Dutch guidelines for pharmaco-economic research, (b) Z-index.

Supplementary Table 4

Within- and between-group differences in dietary intake, after 12 months

	Within-group				Between-group	
	NUTRITION		PLACEBO			
Measure	**adj. M (SE)**	**Z**	**adj. M (SE)**	**Z**	**adj. M (SE)**	**Z**
Energy (kcal)	-78.76±108.06	-0.73	99.44±111.07	0.90	-178.20±153.30	-1.16
Protein (g)	-4.45±4.19	-1.06	6.08±4.30	1.42	-10.53±5.84	-1.80
Carbohydrate (g)	4.29±12.13	0.35	-1.73±12.43	-0.14	6.02±17.31	0.35
Fat (g)	-2.41±5.35	-0.45	7.86±5.52	1.42	-10.27±7.62	-1.35
PUFA (g)	-0.77±1.19	-0.65	-0.86±1.23	-0.70	0.09±1.67	0.05
Cholesterol (mg)	-13.68±16.47	-0.84	53.62±16.83	3.19**	-67.48±22.48	-3.00**
Dietary fiber (g)	0.68±1.01	0.68	0.54±1.03	0.52	0.14±1.44	0.10
Calcium (mg)	-38.28±67.41	-0.57	97.01±68.80	1.41	-135.29±94.04	-1.44
Vitamin A (µg)	-56.46±87.17	-0.65	155.27±88.42	1.76	-211.73±109.37	-1.94
Vitamin C (mg)	3.93±9.00	0.44	11.34±9.26	1.22	-7.41±12.27	-0.60
Vitamin D (µg)	-0.82±0.58	-1.41	0.17±0.59	0.28	-0.98±0.78	-1.26
Vitamin E (mg)	-0.92±1.28	-0.72	-0.47±1.31	-0.36	-0.45±1.64	-0.27

*PUFA: polyunsaturated fatty acids. ** p<0.01.*

Chapter 3

Motivational regulations and lifestyle in patients with COPD and low muscle mass before and after pulmonary rehabilitation

Martijn van Beers
Jessie J. M. Meis
Coby van de Bool
Annemie M. W. J. Schols
Stef P. J. Kremers

Submitted

Chapter 4

Cognitive impairment in chronic obstructive pulmonary disease: disease burden, determinants and possible future interventions

Martijn van Beers
Daisy J. A. Janssen
Harry R. Gosker
Annemie M. W. J. Schols

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Abstract

Introduction: Cognitive impairment (CI) is an important but under-recognized extra-pulmonary feature of chronic obstructive pulmonary disease (COPD). It is related to the burden of disability, worse health outcomes, and impaired self-management.

Areas covered: CI includes deterioration of a wide range of cognitive functions, such as memory and various executive functions. Risk of hospitalization might be higher in patients with COPD compared to those without, with CI negatively impacting the wellbeing of patients with COPD. Disease-specific factors such as hypoxemia and inflammation, lifestyle factors such as dietary insufficiencies and lack of physical activity, and comorbidities such as obstructive sleep apnea and depression are likely to synergistically contribute to the development of CI in COPD. Tailored interventions can possibly improve CI in COPD, but this needs further investigation.

Expert commentary: Further research is warranted involving the optimization of neuropsychological testing for screening and outcome assessment, longitudinal studies to investigate the development of CI in COPD over time, and randomized clinical trials to test the feasibility and efficacy of promising interventions.

Introduction

Chronic obstructive pulmonary disease (COPD) is a chronic lung disease characterized by persistent respiratory symptoms and airflow limitation due to airway and / or alveolar abnormalities (1). It is well established that common extra-pulmonary comorbidities such as heart failure, osteoporosis and muscle wasting contribute significantly to the disease burden (2). Moreover, recent research shows that cognitive impairment (CI) is also a common and important, yet under-investigated comorbidity (3). This review will discuss various aspects related to CI in COPD: its prevalence and characteristics, related health outcomes, determinants, and possible interventions to maintain or improve cognitive functioning in patients with COPD.

Cognitive functioning

Cognition can be defined as any brain function that enables an individual to perceive, register, store, retrieve and use information in order to adapt behavior to new situations and function in our environment (4). Cognition consists of many separate domains, including memory, working memory and attention (5).

Cognition is organized hierarchically and different cognitive functions can be classified as 'lower' or 'higher' (6) (see Figure 1). The lower functions form the basis for the higher functions, including the executive functions such as inhibition (choosing an option that is more rewarding in the longer term instead of the more immediately satisfying option when presented with a choice, for example refusing the attempt to smoke a cigarette) and cognitive flexibility (being able to swiftly shift mental resources, for example changing the type of physical activity undertaken in case of weather changes) (7). Executive functioning in turn underlies even more complex processes such as problem solving and decision making, for example when and how to undertake action in case of increased symptom severity (e.g., disease exacerbation or unintended weight loss).

Specific brain areas do not exclusively perform a single task, but many brain areas are specialized for certain types of tasks (see Figures 2 and 3). The language and memory systems are largely located in the temporal lobe, whereas the higher-order functions such as inhibition, cognitive flexibility, reasoning and decision-making are processed in the frontal lobe. Subcortical structures are located within the brain, including the hippocampus, which plays a central role in memory encoding; the limbic system, including the amygdala and cingulate cortex, which are involved

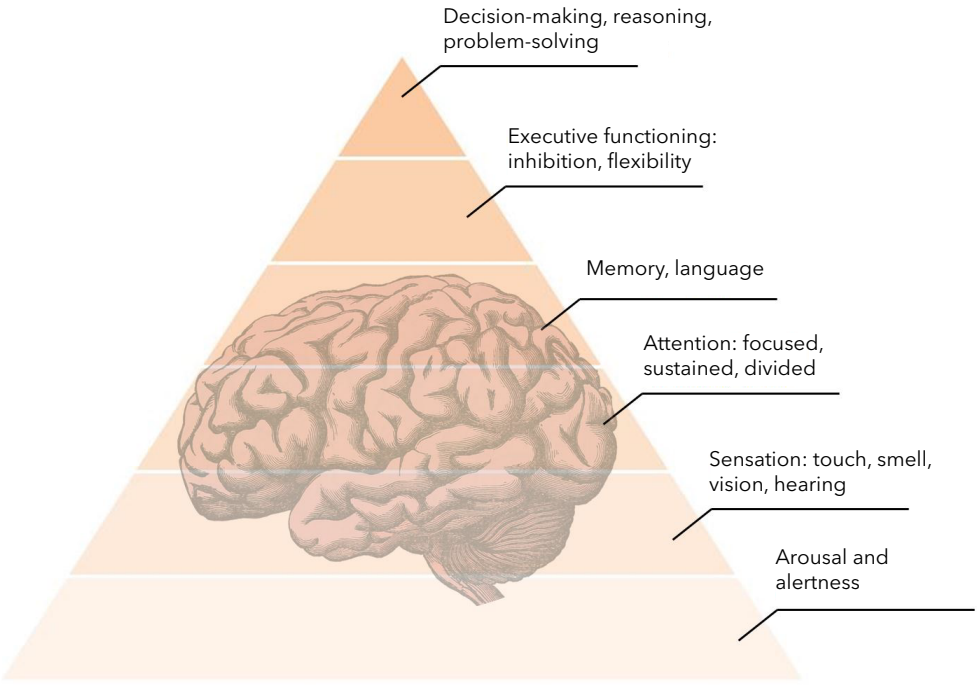

Figure 1

A hierarchical view of cognitive processes. Adapted from Cleutjens et al. (4).

in fear and pain processing; and the basal ganglia, including the caudate nucleus, which is involved in movement but also in learning and remembering (8).

Brain damage, for instance caused by brain atrophy or degeneration, can contribute to the development of CI. This is an inevitable part of aging, but acute and chronic disease can accelerate it. In the initial stages of CI development, impairments are noticeable, but not severe enough to impair activities of daily living; a stage called mild cognitive impairment (MCI) (5). MCI often, but not always, involves impairments in memory rather than in other domains (9), and it may progress into Alzheimer's disease (9) or remain stable (10).

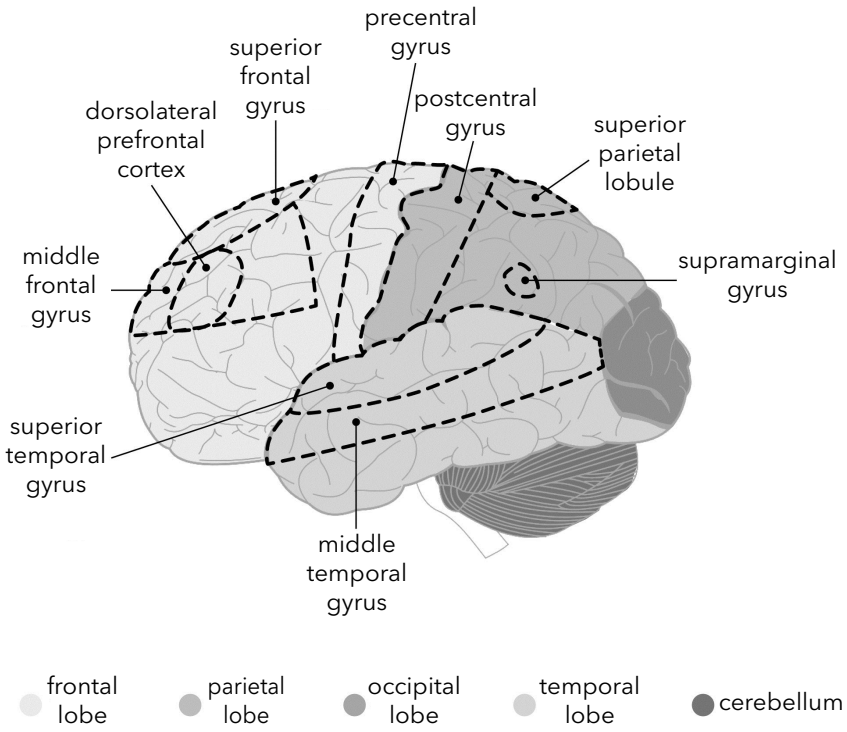

Figure 2

View of the left cerebral hemisphere, indicating the areas mentioned in the text. Adapted from Patrick J. Lynch, medical illustrator, and Carl C. Jaffe, MD, cardiologist.

Cognitive impairment in COPD

Patients with COPD display impairment in cognitive domains as diverse as attention, executive functioning (3, 11-13), (visual) memory and reproduction (14, 15), problem solving, concentration, logical and abstract reasoning, planning, coordination and organization (3). Thus, the pattern of impairments is diffuse, and not every patient is affected or suffers from CI to the same degree in different cognitive domains (16). This diffuse pattern resembles aging-related cognitive deterioration and is consistent with the view of CI in COPD as a manifestation of accelerated ageing (3). On the other hand, patients with Alzheimer's disease or other dementias show a much more specific pattern of CI.

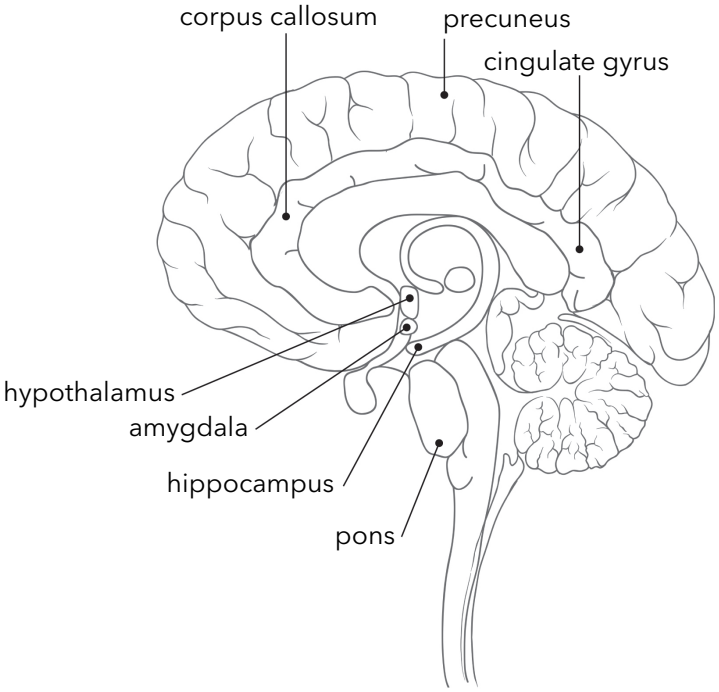

Figure 3

Sagittal view of the brain, indicating the areas mentioned in the text. Adapted from Patrick J. Lynch, medical illustrator, and C. Carl Jaffe, MD, cardiologist.

Prevalence

Cross-sectional studies

A recent meta-analysis pooled 14 studies investigating the prevalence of CI in COPD patients (17). The average prevalence of any CI (5 studies, *N*=2,995) was 32%. MCI was present in 25% of patients (11 studies, *N*=4,663). Higher prevalence of CI was associated with respiratory disease severity, dependence in activities of daily living and poor quality of life (17).

Studies published after this meta-analysis (25 February 2016) show an even higher prevalence of CI (see Table 1). Two studies by Cleutjens *et al.* reported CI, determined by extensive neuropsychological assessment, in 56.7% and 41.5% of patients with COPD referred for pulmonary rehabilitation (PR) (18, 19). In the former

Table 1

Overview of studies investigating the prevalence of CI in COPD

Study	Country	Design	Setting	Population	Sample size	Gender (% male)	Age (M±SD)
Cleutjens, 2017a (18)	Netherlands	cross-sectional	PR	Clinically stable COPD admitted to PR	90	54.4	63.7±8.8
Cleutjens, 2017b (19)	Netherlands	cross-sectional	PR	Clinically stable COPD admitted to PR	76	60.5	62.7±8.7
				Non-CI controls with COPD	107	47.7	63.7±9.9
Cleutjens, 2017c (61)	Netherlands	cross-sectional	PR	Clinically stable COPD admitted to PR	157	50.3	62.9±9.4
Lopez-Torres, 2016 (25)	Spain	longitudinal	hospital	Patients hospitalized with and recovering from acute COPD exacerbation	62	75.8	68.3±7.4
Pierobon, 2017 (20)	Italy	observational, cross-sectional	PR	Stable (no exacerbation for the last 3 months) COPD patients with GOLD stage II-IV, group C-D	84	75.0	70.2±7.0
Park, 2018 (27)	USA	observational, longitudinal	NETT	Radiological evidence of bilateral emphysema, severe airflow obstruction and hyperinflation, and the ability to complete PR	307	59.6	66.2±5.7
Roncero, 2016 (21)	Spain	cross-sectional	respiratory medicine department	Ambulatory patients > 40 years with stable COPD	940	81.6	67.6±10.0
Samareh Fekri, 2017 (23)	Iran	cross-sectional	medical university	Patients with a history and symptoms of COPD	87	90.8	60.5±9.8
				Controls without COPD and CI	60	68.3	58.2±9.8

Table 1 (continued)

Study	Cognitive tests used	Criteria / cut-off for CI	% MCI	% ACI
Cleutjens, 2017a	Comprehensive neuropsychological test battery	Score less than 1SD below age-, gender- and education-specific mean of the MAAS study (24) on 2 subtests or more		56.7% (COPD) 13.3% (controls)
Cleutjens, 2017b	Comprehensive neuropsychological test battery	Score less than 1SD below age-, gender- and education-specific mean of the MAAS study (24) on 2 subtests or more		41.5%
Cleutjens, 2017c	Comprehensive neuropsychological test battery; MMSE	Score less than 1SD below age-, gender- and education-specific mean of the MAAS study on 2 subtests or more; MMSE < 24		5.7% (MMSE); 38.2% (test battery)
Lopez-Torres, 2016	MoCA	MoCA < 20		48.3% (exacerbating) 23.6% (discharge) 36.3% (stable)
Pierobon, 2017	MoCA; MMSE	MoCA performance within bottom 5% of the population		9.5%
Park, 2018	TMTB	Score more than 1.5SD above the normative mean of the current study (134.66s for those with < 12 years of education; 81.09s for those with less)		32.6%
Roncero, 2016	MMSE	MMSE < 27	39.4%	
Samareh Fekri, 2017	MMSE	Mild: MMSE 19-23 Moderate: MMSE 10-19 Severe: MMSE < 10	44.82% (COPD) 33.33% (controls)	6.89% (moderate CI, COPD) 3.33% (moderate CI, controls)

Table 1 (continued)

Study	Miscellaneous methodological remarks
Cleutjens, 2017a	Cognitive scores are split into different domains and composite scores are made
Cleutjens, 2017b	Cognitive scores are split into different domains and composite scores are made
Cleutjens, 2017c	Cognitive scores are split into different domains and composite scores are made
Lopez-Torres, 2016	Different numbers are given for gender and age distribution in the table compared with the figures. Different MoCA versions were used in order to eliminate practice effects; patients with dementia were excluded.
Pierobon, 2017	Patients with MMSE < 18.3 were excluded
Park, 2018	In- and exclusion criteria for the NETT trial did not specifically have cognitive research in mind: neurological disorders or medication which could affect cognition were not excluded, for instance
Roncero, 2016	
Samareh Fekri, 2017	Unconventional CI cut-offs; skewed gender distribution (91% men in the COPD group); many participants had an opium addiction or history of baking in traditional furnaces; non-smoking history was three times more common in the control group compared to the COPD group (36.7% versus 12.6%)

Studies included in the meta-analysis by Yohannes et al. (17) are not included in this table. CI: cognitive impairment; COPD: chronic obstructive pulmonary disease; GOLD: Global Initiative for Chronic Obstructive Lung Disease; MAAS: Maastricht Aging Study; MMSE: Mini-Mental State Examination; MoCA: Montreal Cognitive Assessment; NETT: National Emphysema Treatment Trial; PR: pulmonary rehabilitation; SD: standard deviation; TMTB: Trail Making Test, part B.

study only 13.3% of non-COPD age-matched controls suffered from CI. Pierobon *et al.* showed that the Montreal Cognitive Assessment (MoCA) score of 9.5% of patients admitted to PR was below the 5th percentile of a normal reference group, and only 38.1% scored higher than the median (20). This may be related to the fact that patients referred for PR generally have moderate to advanced disease. Roncero *et al.* showed CI in 39.4% of stable COPD patients. This study was large (*N*=940), but it only assessed cognition using the Mini-Mental State Examination (MMSE) (21), which is useful as a screening tool but not as a diagnostic tool (22). Samareh Fekri *et al.* likewise administered the MMSE to 87 COPD patients and 60 age- and gender-matched individuals. MCI was present in 44.8% of patients with COPD and moderate CI in 6.9%, compared to 33.3% and 3.3%, respectively, in controls (23). It is not reported whether these percentages differ significantly, but the mean MMSE score in the COPD group was significantly lower than in the control group (22.51±2.4 versus 23.63±2.8, respectively).

Lopez-Torres *et al.* investigated cognition during hospitalization for an exacerbation, at discharge and after return to a stable state (25). Cognitive functioning measured by MoCA scores increased significantly from hospitalization to discharge and decreased again from discharge to stable state, but to a higher level than at hospitalization.

In summary, a wide range of prevalences is reported for CI in COPD. The heterogeneity of applied cognitive tests and cut-off points to define CI as well as diverse study populations (community-dwelling, pulmonary rehabilitation, hospitalized patients et cetera) likely contributes to this wide range.

Longitudinal studies

Future research using longitudinal designs may elucidate the development of CI in COPD over several years and the influence of disease progression and other factors in different disease stages. The longitudinal studies already conducted have shown some interesting results. A self-reported diagnosis of COPD in midlife increased the risk of developing CI later in life (odds ratio [OR] 1.85, 95% confidence interval [CI95] 1.05-3.28), but COPD diagnosed later in life was non-significantly inversely related to CI (OR 0.30, CI95 0.08-1.24) (26). This surprising result might be explained by survival bias rather than the effects of COPD itself (26). In a recent study 32.6% of patients taking part in the National Emphysema Treatment Trial (NETT) were impaired on part B of the Trail Making Test (TMT) at baseline (27). This test measures task switching, which is part of executive functioning. No prevalence estimates were given for subsequent time points, but TMT-B performance was virtually unchanged over the 3-year follow-up. Most

remarkably, the sample could be distinguished into four clusters based on their trajectories of cognitive development over three years. One cluster (35.5%) had low baseline TMT-B scores and improving scores over time, the second (39.7%) had low baseline and worsening scores, the third (18.2%) had high baseline and worsening scores, and the fourth (6.5%) had high baseline and improving scores.

Cerebral abnormalities

CI is associated with global and/or specific cerebral abnormalities, and many studies have found structural or functional abnormalities in patients with COPD, along with elevated serum levels of S100B, a putative marker for brain damage (28).

Cortical degeneration (29-32), increased occurrence of small vessel disease (33) or abnormal functional activation on a global level is uncommon in COPD, with a few exceptions. Two studies found overall increased white matter (WM) lesion volumes and decreased WM integrity (30, 31), and cortical thickness and volume were globally reduced in patients who were hospitalized for 30-45 days following an exacerbation (34).

Regional changes are more common. Gray matter (GM) was found to be decreased in many brain regions in both hemispheres, among others in the dorsolateral prefrontal cortex (34), which is involved in higher functions and working memory (35); different areas involved in visuospatial processing (36); the frontal cortex; and limbic and paralimbic structures (15, 29), which are mainly involved in emotion processing and memory (37). Disease duration was inversely related to GM volume in various, mainly subcortical, regions (12, 29), but not in others, including the hippocampus and amygdala (29).

Reduced WM integrity in the superior and middle frontal gyri and right occipital subcortical WM was shown in patients with moderate COPD (32). WM integrity was more reduced in the bilateral frontal subcortical areas, right temporal lobe and pons in severe compared to moderate COPD. Patients with an acute exacerbation who had been hospitalized for several weeks also showed reduced WM integrity compared to healthy controls in various (para)limbic regions (12). However, Cleutjens *et al.* (33) showed that cognitively weak and cognitively strong patients with COPD had equal amounts of WM hyperintensities (WMH).

Two studies investigated the relation between lung function and brain volume in healthy elderly. One study reported a significant correlation between forced expiratory volume in 1 second (FEV_1) and overall brain atrophy and ventricle-to-brain ratio in men but not in women (36). The FEV_1/forced vital capacity (FVC)

ratio was correlated with WMH in the sample as a whole. Participants with and without chronic respiratory disease did not differ on any clinical or brain imaging parameter. Moreover, no control variables were included. The second study only showed a significant positive relationship between FEV_1 and cerebellar WM volume, but no generalized cortical degeneration (39).

The hippocampus is interesting as it is vital in memory formation and learning, and only one of the two regions to display neurogenesis in the adult human brain (40). As such, decreased hippocampal volume could also indicate abnormalities in brain plasticity in patients with COPD, but findings are mixed. In one study, hippocampal volume was decreased in COPD compared to healthy controls and its size was related to partial oxygen pressure and oxygen saturation (41). Hippocampal volume did not differ between patients with mild-to-moderate COPD and those with severe COPD (41). In another study, however, hippocampal volume was not significantly different between patients with COPD and controls (42), and it has also been shown to not differ between cognitively strong and cognitively weak patients with COPD (33).

Functional abnormalities were reported in the left precentral and postcentral gyri and the left caudate nucleus when comparing patients with COPD with controls matched on age, sex and education (14). Evidence on resting state network and default mode network activity is mixed. These networks are distinct from others because their activity increases when the brain is not engaged with other tasks (43). Their increased activation could hinder cognition by interfering with task-related activity. One study found increased resting state network activity in patients with COPD compared to healthy controls, but this result was not significant anymore after controlling for oxygen saturation (14). Another study also found increased default network activation in patients with moderate COPD, but decreased activation in those with severe COPD (44). This result might reflect a compensatory response to damage inflicted by factors associated with COPD, and this response might be strongest in patients with moderate COPD (44).

The structural and functional abnormalities discussed above reflect a gradual influence of COPD on the brain. However, COPD can also heighten the risk of more acute events, such as stroke. This is likely due to high levels of systemic inflammation and oxidative stress, possibly as a result of smoking, leading to endothelial dysfunction, decreased vascular reactivity, thickening of the carotid artery wall and atherosclerotic plaque rupture (45). An elevated risk of stroke in patients with COPD was found in several studies (hazard ratios [HRs] 1.09 [CI95 0.91-1.31] and 1.24 [CI95 1.19-1.28]) (46, 47) and meta-analyses (HRs 1.30 [CI95 1.09-2.09]) (48, 49). The significance in the latter study was probably due to the

large sample size (*N*=132,017 versus 1,566 in the former). HRs are roughly equal for the ischemic, hemorrhagic, intracerebral and subarachnoid hemorrhagic subtypes. However, in the weeks after an acute exacerbation, the HR increased to 6.66 (CI95 2.42-18.20) (46).

In conclusion, patients with COPD show an increased prevalence of many different types of cerebral abnormalities, compared to healthy controls. Patients with COPD have reduced gray and WM volume in various brain areas and WM integrity is compromised. It is still equivocal whether hippocampal volume is decreased in patients with COPD. There is evidence for abnormal functional activation, particularly in the resting state and default mode networks. The abnormalities are spread throughout the brain rather than concentrated in one or some areas. This could possibly explain the diffuse pattern of CI found in COPD.

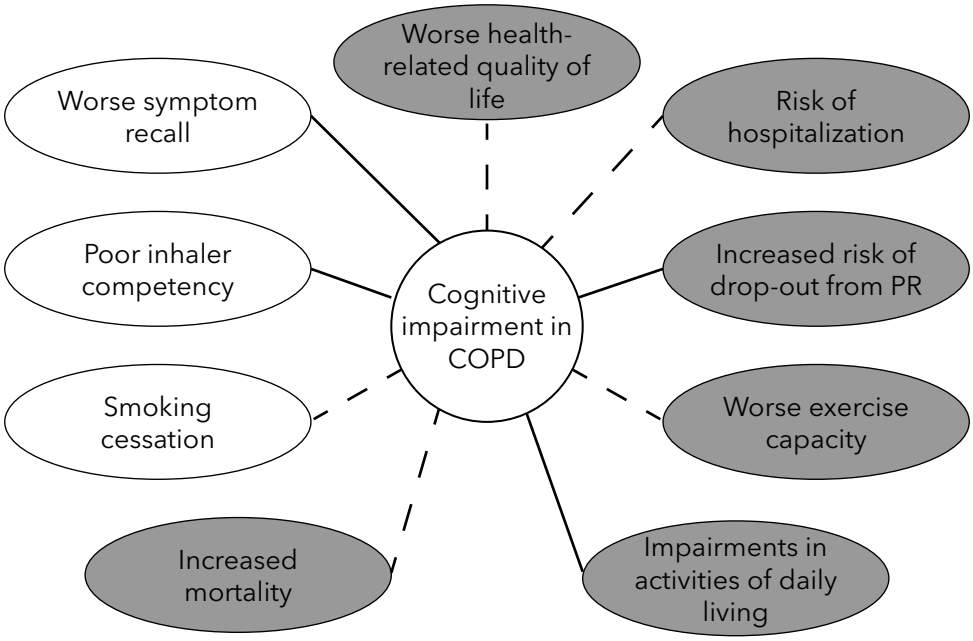

Figure 4

The possible relationships between cognitive impairment and clinical outcomes. Dotted lines represent conflicting literature concerning the relationship.

CI and health outcomes in COPD

CI has a wide range of adverse effects on self-management skills and other health outcomes in patients with COPD (see Figure 4).

Self-management skills

Self-management skills are of major importance for patients with COPD. Symptoms may vary from day to day and increased symptoms may be caused by exacerbations. Patients need to recognize and act upon these exacerbations in an adequate manner (50). Moreover, patients need to adhere to their medication and need to adopt a healthy lifestyle, including a healthy diet and physical activity. Smokers need to quit smoking. This often requires a behavior change, which poses a demand on cognitive functioning (50). It is therefore feasible that CI limits the ability to cope with the daily challenges of living with COPD.

A recent systematic review revealed that there was just one study in which the impact of CI on self-management skills in patients with COPD was investigated (51). This particular study, including 100 participants with COPD, showed no relationship between cognitive functioning assessed with the MoCA and overall self-management abilities, as measured by the Self Management Ability Score 30 (SMAS30). SMAS30 assesses the following: taking initiatives, investment behavior, variety, multifunctionality, self-efficacy, and positive frame of mind. Moreover, living alone affected the interaction between cognitive functioning and self-management abilities (52). In fact, only among patients who lived alone, better cognitive functioning was related to lower self-management abilities (52). Emotional intelligence (defined as the capacity to understand and manage personal thoughts and feelings, as well as to positively influence interpersonal communication and social well-being), however, seems to be related to self-management abilities in COPD (53).

Meek *et al.* (54) showed a relationship between MMSE scores and the ability to accurately recall severity of fatigue and dyspnea in the previous two weeks. It is reasonable to assume that this might impact on the ability to recognize and act upon symptoms of an exacerbation, but the exact relationship remains unknown.

The relationship between CI and inhaler competency is well-known (51). An MMSE score of 23-24 points or less is predictive of poor inhaler technique, as are impaired executive functioning and impaired praxis. While some inhalers may be more difficult to use than others, recognizing CI is of major importance when prescribing inhaler devices as well as providing instructions to use them (51). Some studies suggest Turbohalers might be easier to use for patients

with CI than metered dose inhalers (51, 55). To our knowledge, however, there are no recommendations specifically on inhaler use for COPD patients with CI. Nevertheless, inhaler competency is a major consideration when prescribing inhalers and should be checked regularly.

Brega *et al*. (56) showed that older persons with impaired executive functioning were less likely to quit smoking than those with normal executive functioning. However, recent data did not confirm the relationship between executive cognitive dysfunction and smoking cessation (57). Moreover, another study even showed that persons over 75 years of age who quit smoking had lower cognitive functioning than persons who continued smoking (58). Differences in findings about the relationship between smoking and cognition might be explained by the fact that patients in the last study were older and different methods were used to assess cognitive functioning. Cleutjens *et al*. did not find a statistically significant difference in smoking status between patients with COPD entering PR with or without CI (19). Therefore, whether and to what extent CI limits the ability of patients with COPD to quit smoking remains unclear.

Health outcomes

CI seems related to functional exercise capacity as measured by 6-minute walking distance (59, 60). Nevertheless, this was not confirmed among patients entering PR (19) or during an exacerbation (59).

Cleutjens *et al*. showed that the response after completion of a PR program was similar in patients with CI compared to those without (61). However, patients with CI were more likely to drop out compared to those without CI (23.3% versus 10.3%, respectively). Therefore, timely recognition of CI in patients entering PR seems paramount.

Several studies showed an inverse relationship between CI and HRQoL as assessed with the COPD Assessment Test (21, 60), the EuroQoL-5 dimensions questionnaire (21), or St George's Respiratory Questionnaire (22). Then again, other studies did not confirm this relationship (19, 62).

The systematic review of Baird *et al*. included four studies exploring the relationship between CI and disability and showed that CI is related to impairment in basic activities of daily living, instrumental activities of daily living, work and social activities (51). Martinez *et al*. found that COPD and CI have independent but additive effects on disability (63).

The co-existence of CI and COPD is associated with a more than fourfold increased risk of hospitalization for respiratory-related illnesses and a 34% higher risk of all-cause hospitalization compared to healthy controls, after controlling for various sociodemographic variables, smoking status and comorbidities (64). Moreover, CI seems to be related to an increased length of hospitalization (22). Data from the NETT trial did not show an association between impairment in executive functioning and frequency of hospitalization (65).

A study including stable patients with COPD even showed that drawing impairment predicted increased mortality risk (66). Nevertheless, Yohannes *et al*. found that MMSE scores did not predict 1-year all-cause mortality (67). Moreover, only a modest association was found between executive function and survival in the NETT trial (65).

In conclusion, CI may negatively impact self-management and health outcomes in COPD, but the current literature is conflicting and many questions remain. The conflicting literature may be explained by different methods used to assess cognitive functioning and criteria used to define CI. Moreover, there were major differences between the studied populations. The complex cause-effect relationships also make this field very challenging. COPD may influence self-management skills, but poor self-management in turn also worsens COPD disease progression, thereby creating a vicious cycle.

Determinants of COPD-induced cognitive impairment

Factors such as hypoxemia, hypercapnia, inflammation and lifestyle factors may all contribute to structural and functional cerebral abnormalities and CI. Any individual factor probably does not explain a significant amount of CI, but their synergistic effects may be large (11, 68).

Hypoxemia and hypercapnia

Hypoxemia and hypercapnia are hallmarks of severe COPD (69) which can also negatively affect cognition (70, 71). Hypoxemia alters the microenvironment around neurons (72) and induces impairments in spontaneous and task-stimulated neuronal activity (73, 74). Hypoxemia might underlie decreases in GM density (12, 15), and mild hypercapnia decreases functional connectivity in almost all brain lobes (75). The exact mechanisms through which this happens are still unclear (75). Diminished vasodilatation in response to hypoxemia or hypercapnia in patients with COPD might be one (76).

Inflammation

Multiple lines of evidence indicate that systemic inflammation might underlie CI in COPD. Low-grade systemic inflammation is linked to decreased cognition in other conditions including obesity (77, 78) and metabolic syndrome (79, 80). In the general population c-reactive protein (CRP) and interleukin-6 levels were related to global cognition and executive functioning, whereas α1-antichymotrypsin was not (79). MoCA scores have been found to be negatively correlated with CRP, fibrinogen and erythrocyte sedimentation rate levels (82). The relationship between inflammation and cognition in stable COPD has not been thoroughly investigated yet. Next to low-grade systemic inflammation, patients with COPD may experience periods of an enhanced systemic inflammatory response related to disease exacerbations that will be discussed later.

Respiratory medication

Long-acting β-adrenoreceptor agonists (LABA), long-acting muscarinic antagonists (LAMA) and inhaled corticosteroids are frequently prescribed to patients with COPD (1).

Some literature has associated anticholinergic use with increased risk of MCI (83) and dementia (83-85), and faster cognitive decline (86). However, participants in these studies used systemic rather than inhaled medication. Inhaled medication is much more targeted and will therefore have much less systemic effects. For example, tiotropium cannot cross the blood-brain barrier (87) which might suggest no or limited effect on cognitive functioning. However, no studies have investigated the effects of tiotropium on cognition yet.

The effects of corticosteroids or glucocorticoids (GC) on cognition have not been investigated in patients with COPD yet either. In general, mildly elevated GC levels improve cognition (88), but long-term administration can cause 'steroid dementia', characterized by impairments in episodic, declarative and working memory and executive function, and associated hippocampal and prefrontal dysfunction (89). Steroid dementia can appear within weeks of commencing GC treatment and is largely reversible upon its termination, although impairments can remain for years after termination (89, 90).

It is doubtful whether steroid dementia is a real risk in COPD. The recommended dose and duration for patients with an acute exacerbation (30-40 mg of prednisone daily for 7 to 14 days, where 5 days may be equally effective) (91) are much lower and shorter than those reported to cause steroid dementia (i.e., 60 mg/day for 7 months (90) or 40-60 mg/day for 37 days (92)).

In conclusion, to date, evidence that respiratory medication can contribute to impaired cognition in patients with COPD is lacking.

Exacerbations

During acute exacerbations the above-mentioned determinants intensify and converge. Interestingly, exacerbations have an additional detrimental effect on cognition (22, 82, 92, 93). During acute exacerbations, levels of inflammation and cognitive functioning are inversely related (94), and as recovery from exacerbation-related CI seems very slow to non-existent, it can be speculated that regular COPD exacerbations can trigger a stepwise decrease in cognition. One study found no improvement in the 3 months after an exacerbation (22). However, because these patients were not cognitively tested prior to the exacerbation, it cannot be determined whether the exacerbation actually affected cognition in this study.

Comorbidities

COPD often presents with comorbid conditions such as obstructive sleep apnea (OSA), depression and chronic heart failure (CHF), and a recent systematic review reported an increased risk prevalence of the metabolic syndrome in COPD compared to matched controls (95).

OSA contributes to decreased arterial oxygen saturation (96), causes sleep fragmentation and cortical and sympathetic arousal (96, 97), and affects attention, memory, psychomotor speed, visuospatial abilities, constructional abilities, executive functions and language abilities (96, 98). Hypoxemia, a shared component between OSA and advanced COPD, might underlie the cognitive deficits apparent in both diseases, namely attention, memory, executive function, psychomotor function and language abilities (98).

Depression is associated with decreased cognitive functioning (99) in COPD, but it probably only predicts 1-2% of the variation in cognition (3). A study investigating cognitive bias in patients with COPD and healthy controls with and without depression revealed that depressed patients with COPD showed a comparable pattern of bias compared to depressed healthy controls, whereas never-depressed patients showed much less bias (100). In conclusion, the influence of concurrent COPD and depression on cognition is still equivocal.

Many patients with COPD also suffer from CHF, and *vice versa* (17). The prevalence of CI in CHF is largely unknown, as prevalence estimates between 13.5% and 80% have been reported (17). CHF and COPD might have additive effects on cognition. Moreover, COPD and CHF are both associated with a high prevalence

of cerebrovascular diseases, which could lead to chronic cerebral hypoxia, impaired brain perfusion and ultimately brain damage and cognitive impairment (17). Furthermore, etiological similarities, such as cigarette smoking, may lead to a common set of symptoms, including CI (17).

Metabolic syndrome (MetS) is a cluster of metabolic risk factors, such as central obesity, dyslipidemia, hyperglycemia and dyslipidemia (95), with a prevalence of 34% in patients with COPD (95). MetS is strongly related to the risk of developing type 2 diabetes and cardiovascular disease (95) and has also been shown to have a deleterious influence on cognition (101, 102). However, some research also suggests that certain components of MetS have a larger effect than others (103, 104). It is yet unclear what the relative contribution of each of the components of MetS on cognition is.

Smoking

Smoking is one of the largest risk factors for developing lung cancer or COPD, and it affects cognition in multiple ways. Firstly, it increases carbon monoxide and carbon dioxide levels in the blood, causing hypercapnia (105) and hypoxemia (106), respectively. Secondly, cigarette smoke contains many neurotoxic components, such as cadmium, nitric oxide and lead (107). Thirdly, the many free radicals in cigarette smoke are neurotoxic (108). And finally, chronic nicotine administration increases tau phosphorylation, a key component of Alzheimer's disease pathophysiology (107) and induced free radical production and depleted antioxidant levels in a rat model (109). Ultimately, all of these components cause decreased GM and WM volume and connectivity, and impair cognition (110-112).

Only one study investigated the influence of smoking on CI specifically in patients with COPD (113). Cognitive performance of patients with COPD was comparable to that of smokers, but both were significantly worse compared to normal reference values. The number of pack years and the duration of abstinence of the past smokers, consisting almost two-thirds of the sample, was not reported. Therefore, it cannot be determined with certainty to which degree smoking affects cognition beyond the effects of COPD. In general, smoking per se contributes to cognitive dysfunction, but there is also evidence of a relationship between impaired lung function and cognition independent of smoking (3, 114).

Dietary insufficiencies

Diet and nutritional habits significantly impact on brain fitness, mental and cognitive health throughout life (115, 116). The relative abundance of specific dietary nutrients, depending on intake, bioavailability and metabolism, affects mental

health and cognitive ability via direct and indirect mechanisms that modulate neuronal function and synaptic plasticity (117). Chronic stress has been shown to negatively impact on brain plasticity and cognitive performance, for instance through the harmful effects of cortisol (118-120) and poor dietary habits are hypothesized to correlate with heightened stress reactivity and susceptibility (121) and greater cognitive decline in elderly (122). A healthy diet, rich in polyphenols, B vitamins, polyunsaturated fatty acids and dietary fibers exert favorable effects on cognitive performance, stress reactivity and neuroinflammation (117, 123). Unintended weight loss and muscle wasting is common in advanced COPD, but specific nutritional deficiencies that could affect cognition have received limited attention to date. However, next to disease severity, Collins *et al*. recently highlighted in a UK COPD population the importance of deprivation on malnutrition risk (124). An Australian study reported, next to low muscle mass, a high prevalence of deficiencies in vitamin D, vitamin B12 and iron in patients with COPD hospitalized with an acute exacerbation (125). A Dutch study investigating patients eligible for PR reported that vitamin D and calcium intake were below the recommended levels in more than 75% of patients, whereas vitamin A, C and E intakes were below the recommended levels in over one-third of patients (126). No studies have yet investigated the relationship between nutritional status or dietary pattern and cognitive performance in COPD.

Inactive lifestyle

Higher levels of physical activity are associated with a reduced risk of cognitive decline and dementia (127). However, disease-related factors such as dyspnea and muscular metabolic abnormalities make it hard for many patients with COPD to be physically active. One systematic review found a mean daily step count of 2,237 (128), which is far less than the threshold for a low active (5,000 steps) or active lifestyle (10,000 steps) indicated by the same authors (128). Low physical activity levels and a sedentary lifestyle negatively impact on cognition in the general population (129, 130), and as such may contribute to CI in COPD as well.

Overall, disease-specific as well as lifestyle factors may contribute to the development of CI in COPD, but the relative potential synergistic contributions of the individual factors are yet unclear.

Possible future interventions

Cognitive training

Cognitive training can improve cognitive functioning in healthy elderly adults (131, 132), and can also improve some cognitive domains in those with MCI (131). Research into cognitive training specifically for patients with COPD is scarce. One trial attempted to ameliorate cognition in hypoxemic patients with COPD through an intervention aimed at improving attention, learning and logical-deductive thinking (133). During the first 2 weeks, the intervention group received group cognitive training, in the four weeks thereafter they received individual training, followed by home assignments two times per week. Booster sessions took place after 3 and 5 months. The control group received usual care and no cognitive training. Some cognitive domains improved in both the intervention and placebo group, but the intervention had no additional effect on cognition.

Exercise training

Exercise can improve cognition through multiple pathways. It causes an increase in cerebral blood flow (38) and levels of cerebral growth factors such as brain-derived neurotrophic factor (134) and insulin growth factor-1 (135). These growth factors are involved in many functions which are important for cognition. They influence the rate of differentiation and apoptosis of cerebral cells (136), and regulate long-term potentiation (137) and hippocampal neurogenesis (136). Multiple previous studies have shown the benefit of exercise on cognition in COPD patients (138, 139), and in the study by Park *et al*. the 6-minute walking distance was the only potentially modifiable variable that was related to worsening cognitive functioning over time (27). The question remains, however, whether these improvements consolidate into the longer term if exercise is discontinued (11).

Smoking cessation

Given the deleterious influences of smoking on cognition, it is unsurprising that smoking cessation is beneficial. However, its effects on cognitive functioning have only been assessed in the general population. It appears that the number of pack years negatively affects cognitive functioning, but also that cognitive functioning improves with longer duration of abstinence (140). This implies that abstinence pays off at any age, with the largest benefits coming to those who stop the earliest. Future research should further investigate the effects of smoking cessation on cognition in COPD in more detail.

Dietary intervention

Dietary intervention may imply adopting a different dietary pattern or supplementing the habitual diet with specific nutrients. The Mediterranean diet, the Dietary Approach to Stop Hypertension (DASH) diet and the Mediterranean-DASH Intervention for Neurodegenerative Delay (MIND) diet have been proposed as beneficial to cognition (141-143). Drastic dietary changes, however, are not likely to be feasible for patients with advanced COPD.

These interventions imply that CI in COPD is not something that patients have to passively undergo but can be readily applied in daily life. However, more research is needed to assess the feasibility and efficacy of the individual interventions or multimodalities thereof.

Conclusion

CI in patients with COPD is a problem with a high prevalence and large consequences, yet it is still under-recognized and under-investigated. More research aimed at unraveling the etiology and appropriate interventions to diminish cognitive decline or treat CI in patients with COPD is needed to benefit the patients as well as their loved ones.

Caregivers should pay more attention to potential CI in their patients, as CI may have large consequences on self-management and health outcomes. In a clinical context, administering a brief screening tool may help in identifying patients who need referral to a specialist for further investigation. These patients also need more time and attention, for instance while making sure they understand how to properly use their medication.

Expert commentary

Technical developments in the field of cognitive neuroscience enable more detailed insight in the *pathophysiology* of CI in COPD. Increasing magnetic resonance imaging resolution allows a more detailed picture of the brain, techniques such as diffusion tensor imaging allow focusing specifically on white matter instead of the brain as a whole, and shorter and more effective scanning protocols can make brain imaging more accessible and affordable.

Investigating novel research directions might also be worthwhile. For instance, the synthesis and proper functioning of many neurotransmitters, including the catecholamines, glutamate, aspartate and perhaps most importantly acetylcholine (as it is widely available in the brain but also the most important neurotransmitter in the airways) depend on oxygen availability (144). Hypoxia-based neurotransmitter abnormalities might therefore constitute a third type of cerebral abnormality contributing to CI, next to structural and functional abnormalities. However, this has received scarce research attention to date in the general population, and especially in COPD.

Longitudinal studies are essential for understanding the *causes and consequences* of CI in COPD. They can elucidate the development of cognitive decline in COPD in relation to the development of other potentially relevant variables such as impaired lung function, hypoxia or inflammation. In this way, the relative contributions of disease- and aging-related factors can also be further disentangled.

Interesting *treatment options* for CI in COPD include the potential role of specific nutrients in ameliorating cognition. The Mediterranean diet, which is characterized by a high intake of plant-based foods, moderate-to-high fish and seafood consumption and scarce use of dairy products and meat (141), has earlier been shown to improve cognition in a randomized controlled trial (141). Furthermore, polyunsaturated fatty acids and polyphenols can ameliorate cognition and have a positive effect on various neurobiological processes (145). Also, testing potential synergistic effects of combinations of interventions could be worthwhile, such as exercise training and cognitive training.

An important prerequisite for all the above research questions is the choice of the right cognitive test instruments. Often applied screening tools such as the MMSE or MoCA can be useful in a clinical setting to identify patients in need of further neuropsychological assessment and therapy, but cannot give a detailed overview of the exact nature of a person's deficits. Larger, well-defined and evidence-based test batteries are essential in order to get a comprehensive overview of a person's neuropsychological functioning (146).

Five-year view

In conclusion, it is important to further investigate the pathophysiology, causes and consequences of CI in COPD in the next five years, and to develop tailored intervention strategies. Developments in the fields of cognitive neuroscience and neuropsychology will enable a more detailed picture of the pathophysiology of

CI in COPD. Longitudinal studies can pinpoint its determinants and identify its consequences, and much work remains to be done in finding (the most) effective treatments.

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Chapter 5

Cognitive performance in relation to metabolic disturbances in patients with COPD

Martijn van Beers
Harry R. Gosker
Daisy J. A. Janssen
Fiona A. H. M. Cleutjens
Frits M. E. Franssen
Martin P. J. van Boxtel
Emiel F. Wouters
Rudolf W. H. M. Ponds
Annemie M. W. J. Schols

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Abstract

Background and aims: Cognitive impairment (CI) and metabolic abnormalities, including the metabolic syndrome (MetS) and sarcopenia, are more prevalent in COPD patients compared to controls without diagnosed lung disease. Because earlier studies have shown these metabolic abnormalities may affect cognitive performance, this study investigated whether cognitive performance is more impaired in subgroups of COPD patients with MetS or sarcopenia.

Methods: Cognitive performance patterns of 170 COPD patients referred for pulmonary rehabilitation (53.5% male, 63.4±9.4 years, FEV_1 54.5±22.7% predicted) were compared between COPD subgroups stratified by presence of MetS and sarcopenia. Cognitive performance was assessed using a detailed neuropsychological test battery, which measured psychomotor speed (Stroop Color-Word Test, Concept Shifting Test, Letter-Digit Substitution Test), planning (Behavioral Assessment of the Dysexecutive Syndrome), working memory (Visual-Verbal Learning Test, Digit Span), verbal memory (Visual-Verbal Learning Test) and cognitive flexibility (Stroop Color-Word Test, Concept Shifting Test). MetS was determined according to the NCEP ATP-III criteria. Sarcopenia was determined based on decreased appendicular lean mass by dual-energy x-ray absorptiometry and impaired physical performance by 6-minute walking distance.

Results: MetS was observed in 54.7% and sarcopenia in 30.0% of COPD patients. The prevalence of general CI was not different between patients with and without MetS (30.4% and 39.0%, respectively) or those with and without sarcopenia (34.0% and 34.5%, respectively, both $p>0.05$). Domain-specific cognitive performance was not different between metabolic subgroups, but those with sarcopenia displayed a lower prevalence of CI on verbal memory than those without (21.7% and 29.7%, respectively, $p=0.011$). Only the digit span (working memory) subtest was significantly different between metabolic subgroups, in favor of those without MetS ($p=0.017$).

Conclusion: Cognitive performance was not affected more in COPD patients with sarcopenia or MetS.

Introduction

Chronic obstructive pulmonary disease (COPD) is often associated with systemic manifestations including metabolic syndrome (MetS) and sarcopenia (1, 2). Cognitive impairment (CI) is also a common, yet often overlooked, comorbidity of COPD, with a recent meta-analysis reporting a 32% prevalence (3). CI in COPD has been associated with lower quality of life (4), a higher need for assistance in aspects of daily living such as medication adherence and self-management (5) and a higher risk of all-cause hospitalization (hazard ratio [HR] for patients with COPD and CI compared to controls without COPD and CI 1.34 [95% confidence interval 1.00-1.80]; HR for patients with COPD but no CI compared to controls without either 1.24 [95% confidence interval 1.06-1.45]) (6), and hospitalized patients with COPD scored significantly worse on a range of cognitive tests compared to their stable counterparts (7). Moreover, patients with CI dropped out of pulmonary rehabilitation (PR) twice as often as those without (23.3 versus 10.3%) (8). Although the etiology of CI in COPD remains largely unknown, it can be speculated that metabolic comorbidities adversely affect cognition in these patients because of shared lifestyle-related risks.

MetS is a cluster of cardiovascular risk factors which, according to a recent review, affects 34% of patients with COPD, a significantly higher proportion than among healthy controls with a comparable body mass index (BMI) (1). MetS is related to reduced levels of multiple indices of cerebral (9, 10) and blood-brain barrier integrity (11) and a reduced blood oxygenation level-dependent (BOLD) imaging signal in frontal and parietal regions (12) in community-dwelling older adults. MetS is also associated with impaired working memory and episodic memory (13), attention and executive functions (13, 14) in healthy elderly, although one study only found significant results in men (13). Some evidence has been found for a dose-response relationship, in which a higher number of MetS symptoms is associated with worse cognitive performance (13). These effects can be long-lasting: in one meta-analysis MetS was associated with a decline in cognitive performance in participants under 70 years old over a follow-up period of up to 16 years (15) and hyperglycemia and insulin resistance have been associated with declines in cognitive performance in a community sample over a 20-year period between ages 53 and 73 (16). The relative contribution of the separate MetS components towards CI remains unclear, although various components or combinations thereof with a significant association with CI have been reported, such as high-density lipoprotein (HDL) cholesterol (17), hyperglycemia (18), waist circumference and hyperglycemia (19), or all components except HDL cholesterol (20).

Sarcopenia is defined as a progressive and generalized skeletal muscle disorder that is associated with increased likelihood of adverse outcomes including falls, fractures, physical disability and mortality (21). It occurs in normal ageing but is more prevalent in COPD (21, 22). In healthy elderly populations, a smaller muscle mass has been associated with lower cerebral volume (23) and diminished white matter integrity (24) which lead to poorer cognitive performance. Interestingly, these cerebral abnormalities have also been shown in COPD (25, 26). Furthermore, in healthy elderly, fat-free mass was found to be related to whole-brain volume (27) and total lean mass has been associated with whole-brain volume and white matter volume (28). In a recent review (29) white matter hyperintensity volume and volumes of various brain areas were related to grip strength, but relationships with gait speed were much weaker. Some studies have found a two- to threefold higher risk of developing CI in healthy participants with low muscle mass (30, 31) or functional impairment, defined as a score on the short physical performance battery of less than 9 (32). In one smaller sample (*N*=34) between 71 and 92 years old, the risk was even found to be three- to 4.5-fold, depending on the definition of sarcopenia (33).

The current study therefore aims to investigate whether the presence of MetS or sarcopenia is related to an elevated prevalence and/or different pattern of CI in patients with COPD referred for PR. Investigating this putative connection is important for timely screening of CI in high-risk groups and to optimize and tailor lifestyle interventions.

Methods

Study design

Cognitive performance of 170 patients with COPD referred for PR was compared between subgroups stratified by sarcopenia or MetS in a cross-sectional design. These patients took part in the COgnitive-PD study (34), which was conducted at CIRO, a center of expertise for patients with chronic organ failure in Horn, The Netherlands, between November 2013 and June 2015. The study was registered in the Dutch Trial Registry (NTR 4215) and approved by the medical ethics committee of Maastricht University Medical Center (NL45127.068.13). The 13 patients who were excluded from the original sample (*N*=183) had missing data on metabolic parameters.

Patients

Patients with COPD were eligible to take part in this study if they had a diagnosis of COPD based on the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines (35). Those with clinically unstable COPD in the past 4 weeks, a diagnosis of dementia or insufficient mastery of the Dutch language were not eligible to participate. All participants gave written informed consent.

The MAAS population was invited from the Registration Network Family Practices, a patient register of collaborating general practitioners, representative of the Dutch population. Participants were excluded if they suffered from major cerebrovascular pathology, a nervous system tumor or congenital malformation, multiple sclerosis, Parkinsonism, epilepsy, dementia, organic psychosis, schizophrenia, affective psychosis or intellectual disability. Participants with a history of diagnosed lung disease were excluded during the matching process. Demographical (age, sex, educational level), clinical (BMI) and neuropsychological test data was gathered during a 3-hour medical and neurocognitive screening visit. All participants gave written informed consent and both studies were conducted in accordance with the Helsinki Declaration.

Measurements

Demographics and lung function

Demographics and lung function (flow volumes and diffusion capacity) of the patients with COPD were assessed during the 3-day assessment at the start of the PR program.

Metabolic risk profile

MetS and sarcopenia parameters were taken in the COPD population from the 3-day assessment at the start of the PR program. MetS was assessed using the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP-III) criteria (36), and the sample was divided into groups with and without MetS based on these cutoffs. Sarcopenia was defined as a combination of low muscle mass and functional impairment (21), based on skeletal muscle mass index (SMI) and performance on the 6-minute walking test, respectively. SMI was calculated as appendicular lean mass (ALM) / height². ALM was determined by dual energy x-ray absorptiometry (DEXA). Low muscle mass was defined as an SMI below 7 kg/m² for men or below 5.5 kg/m² for women, according to Cruz-Jentoft *et al.* (21). Decreased functional performance was defined as a 6-minute walking distance (6MWD) below 80% of the distance predicted using the formula by Troosters *et*

al. (37). Participants with low muscle mass and low functional performance based on these cut-offs were assigned to the sarcopenia group; those not meeting both criteria were assigned to the no-sarcopenia group.

Cognition

Cognitive performance of the patients with COPD was measured using a detailed neuropsychological assessment during a home visit prior to starting PR. See Cleutjens *et al*. (34) for details.

General cognitive performance comprised six test scores: the number of animals named in the animal naming subtest of the Groninger Intelligence Test-II (38), the time to complete card 3 of the Stroop Color-Word Test (39), the time to complete part C of the Concept Shifting Test (40), the number of correct items on the Letter-Digit Substitution Test (41), and the total and delayed recall scores of the Visual-Verbal Learning Test (42).

Performance on five cognitive domains (psychomotor speed, planning, working memory, verbal memory and cognitive flexibility) was assessed using scores on the six tests mentioned above, along with the digit span backwards task (43) and the Behavioral Assessment of the Dysexecutive Syndrome (BADS) (44). See Table 1 for a complete overview.

Sample size calculation

The required sample size was based on a power of 80% and an α of 0.05. The expected effect size was based on a four-point difference on the St George's Respiratory Questionnaire, and a drop-out rate of 10% was taken into account. These parameters resulted in a required sample size of 183. Additional details can be found in Cleutjens *et al*. (34).

Statistical analyses

Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS, IBM Corp., Armonk, NY), version 25. A *p*-value below 0.05 was considered statistically significant.

For cognitive profiling, the patients were individually matched in a 1:1 ratio based on age, sex, educational level and BMI to controls from the Maastricht Aging Study (45) (MAAS; approved by the local medical ethics committee [MEC-05-107]). Additional matching on BMI was done because of established independent effects on cognitive performance (46) and because BMI is often affected in MetS

Table 1

Neuropsychological tests used to determine domain-specific cognitive performance

Test name	**Subscore or subtest**	**Parameter measures**
Psychomotor speed		
SCWT	Card I (time in seconds)	Reading speed
CST	Part A (time in seconds)	Simple motor speed
LDST	Number of correct items in 60 seconds (written and oral)	Psychomotor speed / information processing speed
Planning		
BADS	Key search (profile score: 0-4)	Planning and priority setting
BADS	Zoo map (profile score: 0-4)	
Working memory		
VVLT	Trial 1 (number correct: 0-15)	Immediate verbal span
Digit span	Backward (span: 0-7)	Working memory
Verbal memory		
VVLT	Total recall (number correct: 0-75)	Overall verbal learning and verbal memory after an interval
	Delayed recall (number correct: 0-15)	
	Retention (percentage of words that were retained from the immediate to the delayed score)	
Cognitive flexibility		
SCWT	Card III (time in seconds)	Attentional inhibition of a dominant response
CST	Part C (time in seconds)	Alternating attention

Adapted from Cleutjens et al. (34). BADS: Behavioral Assessment of the Dysexecutive Syndrome; CST: Concept Shifting Test; LDST: Letter-Digit Substitution Test; SCWT: Stroop Color-Word Test; VVLT: Visual-Verbal Learning Test.

and sarcopenia. Matching on BMI prevented the effects of BMI-related metabolic risk to confound the effects of MetS- and sarcopenia-related metabolic risk.

Individual raw cognitive test scores of the patients with COPD were converted into Z-scores using the formula $Z = (X - \mu) / \sigma$, in which X is an individual score, μ is the mean of the 170 MAAS participants and σ is the standard deviation of the 170 MAAS participants (47). Because the BADS and digit span task were not

administered in MAAS, norm values published elsewhere were used (43, 44). General CI was defined as a *Z*-score below -1 on two or more of the six contributing tests; domain-specific CI as a Z-score on a specific domain below -1 (47). Domain-specific cognitive performance scores were obtained by averaging the *Z*-scores of tests belonging to that particular domain.

Within the COPD population, differences on demographic and clinical parameters and cognitive performance were assessed between metabolic subgroups using independent-samples *t*-tests or Mann-Whitney *U*-tests, depending on the distribution of the data. The normality of the distribution was determined using the Kolmogorov-Smirnov test. Differences on categorical variables and prevalence of CI were assessed using χ^2 tests. The influence of smoking status (current/former/never) and the number of pack years on cognitive performance was assessed using analyses of variance and regression analyses, respectively. Smoking status and the number of pack years served as independent variables, the separate cognitive test scores as dependent variables.

Results

Demographical characteristics are presented in Table 2. The study group consisted of 170 patients (53.5% male), aged 63.4±9.4 years, with a BMI of 26.6±5.6 kg/m^2 and moderate to severe airflow obstruction (FEV_1 54.5±22.7% predicted). General CI was present in 58 patients (34.3%) (see Table 3).

The first trial of the Visual-Verbal Learning Test was the only cognitive test with significant differences between current (*n*=146), former (*n*=22) and never-smokers (*n*=2), due to a significantly higher score by the never-smokers (*p*=0.040). Pack years were only significantly related to the zoo map test of the BADS (*p*=0.008) and the VVLT delayed recall score (*p*=0.046).

Metabolic syndrome

The prevalence of MetS was 54.7%. Patients with MetS had a significantly higher BMI (*p*<0.001) and diffusion capacity (*p*=0.006) than those without. All MetS parameters except for systolic and diastolic blood pressure were significantly different between the groups, all in the expected directions. ALM, SMI, fat mass (all *p*<0.001) and 6MWD % predicted (*p*=0.045) were significantly higher in the group with MetS compared to that without (see Table 2).

General CI was present in 28 COPD patients with MetS and in 30 without (prevalence 30.4% and 39.0%, respectively; *p*=0.245) (see Table 3). Cognitive

Table 2

General clinical and demographical characteristics

Variable	**Overall**	**No MetS**	**MetS**	**No sarcopenia**	**Sarcopenia**
General clinical characteristics					
N (male / female) [c]	170 (91/79)	77 (39/38)	93 (52/41)	119 (67/52)	51 (24/27)
Age (years) [b]	63.4±9.4	62.1±10.0	64.5±8.7	63.4±9.6	63.3±9.0
BMI (kg/m²) [a]	26.6±5.6	22.9±4.1	29.7±4.7***	28.8±5.0	21.6±3.5***
Pack years [b]	42.5±24.6	43.0±24.0	42.1±25.2	42.8±24.8	41.9±24.5
6MWD (m) [b]	436.4±109.1	431.2±122.1	440.6±97.6	455.0±104.0	392.9±109.4**
6MWD (% predicted) [b]	68.8±16.2	65.5±17.6	71.5±14.4*	72.4±15.0	60.3±15.9***
Smoking status (current/former/never) [c]	22/146/2	12/65/0	10/81/2	10/109/0	12/37/2**
Lung function parameters					
FEV_1 (% predicted) [a]	54.5±22.7	52.7±26.1	56.0±19.5	60.8±21.2	39.8±19.1***
FVC (% predicted) [a]	100.7±20.8	101.2±24.3	100.2±17.5	104.6±19.0	91.6±22.2***
DLCO (% predicted) [b]	52.4±18.6	48.0±16.0	55.9±19.7**	56.6±18.4	42.4±15.0***
MetS parameters					
Waist circumference (cm) [a]	99.5±16.6	88.4±13.7	108.8±12.7***	104.8±15.0	87.2±13.5***
Fasting glucose (mmol/l) [b]	6.15±1.13	5.76±1.10	6.48±1.06***	6.21±1.03	6.03±1.35*
Triglycerides (mmol/l) [b]	1.50±0.67	1.22±0.45	1.73±0.74***	1.62±0.72	1.21±0.43***
HDL cholesterol (mmol/l) [b]	1.36±0.42	1.47±0.38	1.27±0.42***	1.30±0.41	1.50±0.40**

Table 2 (continued)

Variable	Overall	No MetS	MetS	No sarcopenia	Sarcopenia
Systolic BP (mmHg) [b]	140.5±22.3	134.3±20.1	145.7±22.8**	143.0±22.5	134.8±21.0
Diastolic BP (mmHg) [b]	79.8±12.0	77.9±10.2	81.3±13.2	80.8±11.8	77.3±12.3
Body composition parameters					
FFM (kg) [b]	46.70±10.34	43.24±9.61	49.57±10.08***	49.47±10.10	40.25±7.72***
ALM (kg) [b]	19.85±5.41	18.18±5.08	21.24±5.30***	21.48±5.26	16.05±3.52***
SMI (kg/m^2) [a]	6.94±1.41	6.36±1.27	7.41±1.35***	7.47±1.28	5.70±0.80***
Fat mass (kg) [a]	26.16±11.29	18.96±9.07	32.12±9.32***	29.86±10.47	17.53±7.99***
Fat percentage [b]	33.63±9.70	28.55±10.03	37.84±7.06***	35.84±8.82	28.49±9.75***

*All data given as mean ± standard deviation, unless noted otherwise. Differences between the groups with and without MetS and those with and without sarcopenia were tested using independent-samples t-tests for variables indicated with [a], using Mann-Whitney U-tests for those indicated with [b] or using χ^2 tests for variables indicated with [c]. * p<0.05; ** p<0.01; *** p<0.001. 6MWD: 6-minute walking distance; ALM: appendicular lean mass; BMI: body mass index; DLCO: diffusion capacity of the lung for carbon monoxide; FEV_1: forced expiratory volume in 1 second; FFM: fat-free mass; FVC: forced vital capacity; HDL: high-density lipoprotein; MetS: metabolic syndrome; SMI: skeletal muscle mass index.*

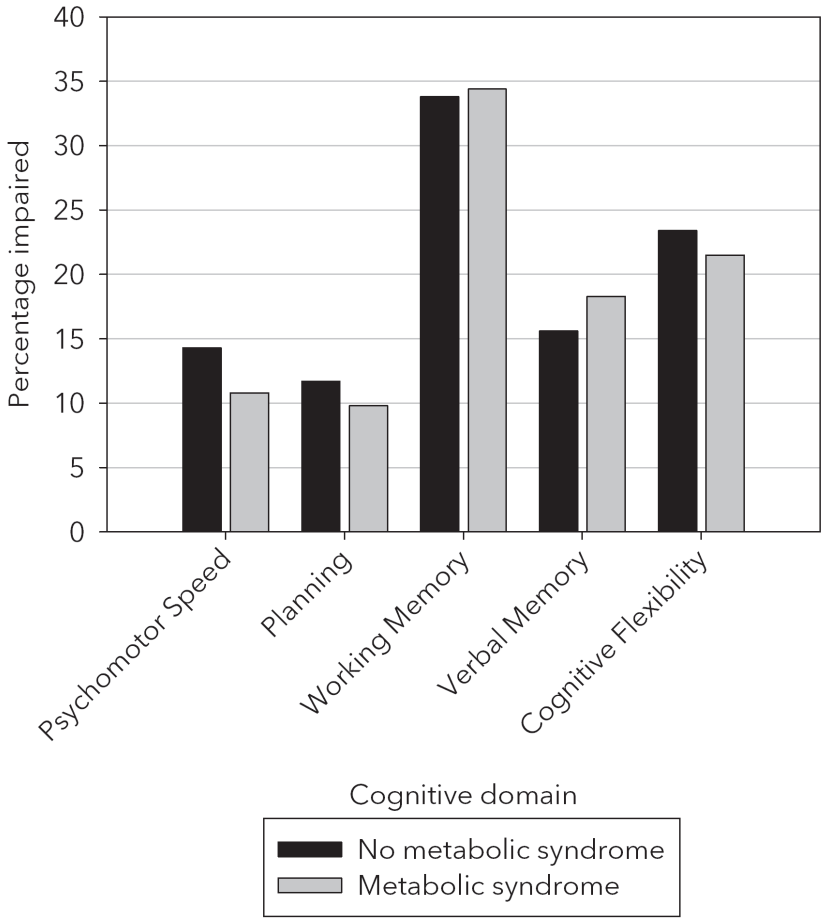

Figure 1

Prevalence of domain-specific CI, divided by MetS status

domain scores (see Table 4) and the prevalence of domain-specific CI (see Figure 1) were not different between the groups with and without MetS. The only significant difference between the groups on the separate cognitive subtests was a better performance on the digit span backwards test by the group without MetS (p=0.017) (see Table 4).

Sarcopenia

The prevalence of sarcopenia was 30.0%. Patients with sarcopenia had a significantly lower BMI (p<0.001) and 6MWD than those without, expressed as

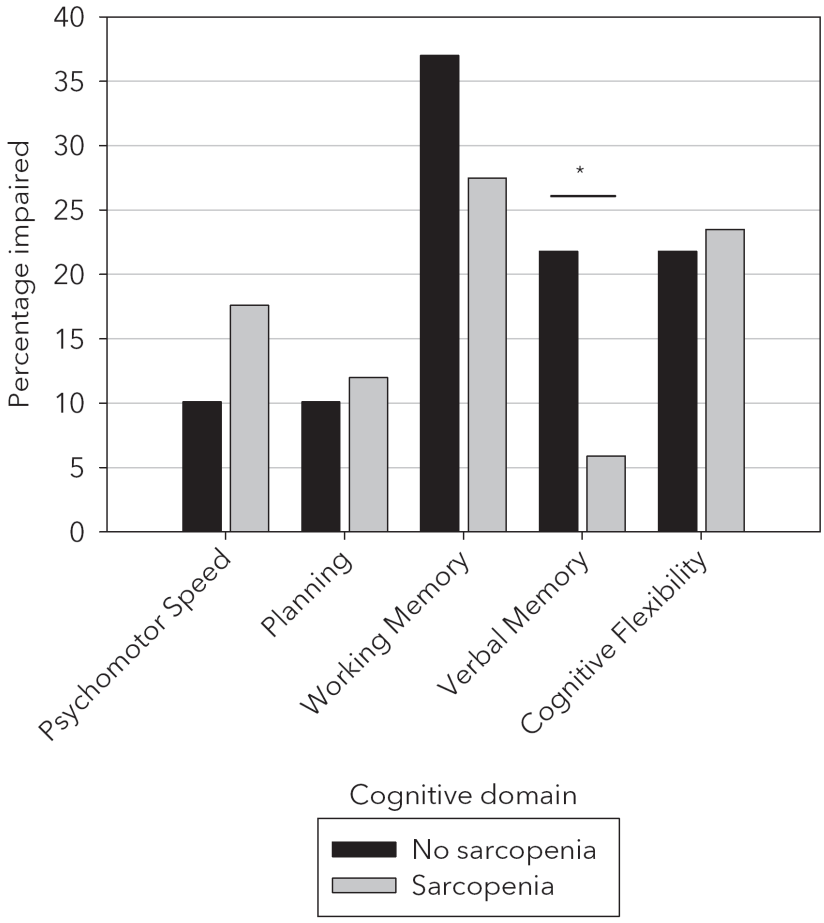

Figure 2

*Prevalence of domain-specific CI, divided by sarcopenia status. * p<0.05.*

absolute values (p=0.001) and percentage predicted (p<0.001). The distribution of current, former and never-smokers was significantly different between the groups, with a significantly higher proportion of current and never-smokers in the group with sarcopenia (p=0.002). All lung function parameters were significantly higher in the group without sarcopenia, indicating better lung function in the patients without sarcopenia (all p<0.001), and all MetS and body composition parameters except systolic and diastolic blood pressure were significantly different between the groups (see Table 2).

Table 3

Cognitive test scores used to determine general CI

Variable	**Overall (*N*=170)**	**No MetS (*n*=77)**	**MetS (*n*=93)**	**No sarcopenia (*n*=119)**	**Sarcopenia (*n*=51)**
Prevalence of general CI (%) [c]	*34.3*	*39.0*	*30.4*	*34.5*	*34.0*
GIT verbal fluency (# of animal names) [b]	22.0±6.7	21.6±6.9	22.3±6.5	22.1±6.6	21.6±7.0
LDST 60 sec oral (# correct) [b]	33.7±7.5	34.3±8.6	33.2±6.5	33.4±7.5	34.4±7.5
VVLT total recall trial 1-5 (# correct) [a]	41.6±11.0	42.6±11.1	40.8±10.9	41.8±11.4	41.3±10.0
VVLT delayed recall (# correct) [b]	7.8±3.6	8.1±3.7	7.6±3.5	7.7±3.8	8.2±3.0
SCWT, card 3 (s) [b]	54.9±21.4 †††	54.7±22.2	55.0±20.9	55.5±23.9	53.4±14.3
CST-C (s) [b]	44.6±22.6	44.9±27.4	44.4±17.9	45.2±23.2	43.3±21.4

All data given as mean ± standard deviation, unless noted otherwise. Differences between the groups with and without MetS and those with and without sarcopenia were tested using independent-samples t-tests for variables indicated with [a], using Mann-Whitney U-tests for those indicated with [b] or using χ^2 tests for variables indicated with [c]. ††† p<0.001 compared to the MAAS population. CST: Concept Shifting Test; GIT: Groninger Intelligence Test; LDST: Letter-Digit Substitution Test; MetS: metabolic syndrome; SCWT: Stroop Color-Word Test; VVLT: Visual-Verbal Learning Test.

Table 4

Cognitive test scores used to determine domain-specific CI

Variable	**Overall (*N*=170)**	**No MetS (*n*=77)**	**MetS (*n*=93)**	**No sarcopenia (*n*=119)**	**Sarcopenia (*n*=51)**
Psychomotor speed (Z-score) [b]	*-0.02±1.12*	*-0.01±1.44*	*-0.02±0.77*	*-0.02±1.16*	*-0.01±1.04*
SCWT, card 1 (s) [b]	17.9±4.5	18.1±5.6	17.8±3.3	18.0±5.0	17.9±3.1
CST-A (s) [b]	25.4±12.6	26.6±17.0	24.4±7.1	25.2±13.3	25.9±11.1
LDST 60 sec read (# correct) [b]	27.4±7.4	28.4±8.2	26.6±6.5	27.4±7.2	27.5±7.8
LDST 60 sec oral (# correct) [b]	33.7±7.5	34.3±8.6	33.2±6.5	33.4±7.5	34.4±7.5
Planning (Z-score) [b]	*-0.05±0.68*	*-0.04±0.67*	*-0.05±0.68*	*-0.05±0.69*	*-0.05±0.66*
BADS key search profile score [b]	2.5±1.4	2.6±1.4	2.5±1.4	2.5±1.4	2.6±1.4
BADS zoo map profile score [b]	2.4±0.8	2.4±0.8	2.4±0.8	2.4±0.8	2.3±0.8
Working memory (Z-score) [b]	*-0.51±0.77*	*-0.45±0.82*	*-0.56±0.73*	*-0.52±0.80*	*-0.48±0.72*
VVLT trial 1 (# correct) [b]	4.7±1.9	4.6±1.9	4.7±1.9	4.8±1.9	4.5±1.8
Digit span backwards (# correct) [b]	3.0±1.1	3.2±1.1	2.9±1.0 *	2.9±1.1	3.3±0.9
Verbal memory (Z-score) [a]	*-0.11±1.02*	*-0.04±1.09*	*-0.16±0.97*	*-0.15±1.08*	*-0.01±0.86*
VVLT total recall trial 1-5 (# correct) [a]	41.6±11.0	42.6±11.1	40.8±10.9	41.8±11.4	41.3±10.0
VVLT delayed recall (# correct) [b]	7.8±3.6	8.1±3.7	7.6±3.5	7.7±3.8	8.2±3.0
VVLT retention score (%) [b]	72.8±25.7	72.7±28.1	72.8±23.6	70.7±26.6	77.5±23.0
Cognitive flexibility (Z-score) [b]	*-0.51±1.39*	*-0.52±1.59*	*-0.51±1.22*	*-0.56±1.51*	*-0.41±1.09*
SCWT, card 3 (s) [b]	54.9±21.4	54.7±22.2	55.0±20.9	55.5±23.9	53.4±14.3

Table 4 (continued)

Variable	Overall (N=170)	No MetS (n=77)	MetS (N=93)	No sarcopenia (n=119)	Sarcopenia (n=51)
CST-C (s) [b]	44.6±22.6	44.9±27.4	44.4±17.9	45.2±23.2	43.3±21.4

*All data given as mean ± standard deviation, unless noted otherwise. Differences between the groups with and without MetS and those with and without sarcopenia were tested using independent-samples t-tests for variables indicated with [a] or Mann-Whitney U-tests for those indicated with [b]. * p<0.05. BADS: Behavioral Assessment of the Dysexecutive Syndrome; CST: Concept Shifting Test; LDST: Letter-Digit Substitution Test; MetS: metabolic syndrome; SCWT: Stroop Color-Word Test; VVLT: Visual-Verbal Learning Test.*

General CI was present in 17 COPD patients with sarcopenia and in 41 without (prevalence 34.0% and 34.5%, respectively; p=0.955) (see Table 3). The prevalence of CI on the verbal memory domain was significantly lower in those with sarcopenia compared to those without (p=0.011) (see Figure 2), but no cognitive domain scores or separate cognitive tests were significantly different between the groups (see Table 4).

Discussion

The current study shows a higher prevalence of MetS and sarcopenia in patients with COPD eligible for PR, than reported earlier in patients with COPD both in and outside of a PR context (1, 48, 49). The prevalence of CI was comparable to that in a recent systematic review (3). There was no different pattern of cognitive performance in the COPD subgroups with MetS or sarcopenia compared to the subgroups without.

MetS and sarcopenia and their separate parameters did not significantly affect cognitive performance in our study group. This does not exclude the possibility that common and shared lifestyle determinants of metabolic and cognitive disturbances in COPD, including physical activity (50, 51) and a low-quality diet (52, 53), may explain the high prevalence of impaired cognitive performance. Although smoking can also affect cognitive performance (54, 55), its influence in the current study was limited. Further research is warranted to disentangle the relative contribution of these modifiable lifestyle factors in the etiology and progression of CI in COPD.

Our results are at odds with earlier research that did associate MetS (56-58) and sarcopenia (59, 60) with poorer cognitive performance in participants without COPD. Other studies found non-significant (61-63) or mixed results (17, 18). These inconsistent results can result from different sources, such as differences in age ranges, in the operationalization of cognitive performance and CI, in the operationalization of MetS or sarcopenia or from lack of sufficient power. Secondly, methodological weaknesses in cognitive screening can distort results. Many previous studies gauged cognition using a single screening tool, which is less sensitive than a comprehensive test battery, or excluded participants with pre-existing CI (e.g., Mini-Mental State Examination score ≤ 24). The use of a screening tool and selectively excluding certain participant groups both reduce variance on cognitive outcome measures and could lead to underestimating effect sizes. Thirdly, not all of the MetS components are equally strongly associated

with cognition (16-18). Also in our sample, only glucose levels were significantly positively related to cognition (data not shown).

Strengths of the current study include the use of a comprehensive neuropsychological test battery, rather than a single screening tool, to investigate cognitive performance. The calculation of *Z*-scores based on case-control matching allowed us to reliably compare cognitive performance of the patient population to controls corrected for known determinants of cognitive functioning.

A strength but also potential limitation includes the fact that our study population consisted of patients in tertiary care. The prevalence of metabolic derangements is high in this population, but many patients have complex pathology and comorbidities, which might limit the generalizability of the results to COPD per se. Secondly, we were unable to control for confounding factors such as socio-economic status or COPD disease duration, following the studies by Cleutjens *et al.* (47) and many others. Thirdly, like most other comparable studies, we were constrained to a cross-sectional study design, which limits our ability to draw conclusions about causality.

In conclusion, COPD subgroups with MetS and sarcopenia exhibited comparable patterns of cognitive performance and impairment relative to those without. Because earlier research has shown poorer cognitive performance in patients with COPD compared to healthy controls, COPD constitutes an indication for cognitive screening, but the presence of MetS or sarcopenia in patients with COPD does not.

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Chapter 6

Efficacy of working memory training in chronic obstructive pulmonary disease: the randomized placebo-controlled Cogtrain trial

Martijn van Beers
Sarah W. Mount
Katrijn Houben
Harry R. Gosker
Lisanne Schuurman
Frits M. E. Franssen
Daisy J. A. Jansen
Annemie M. W. J. Schols

Submitted

Chapter 7

General Discussion

Leading a healthy lifestyle is important for patients with COPD. It benefits their overall health status, for instance through slowing down disease progression. Nevertheless, the lifestyle of many patients with COPD is unhealthy: some of them still smoke, they are often physically inactive (1, 2) and consume an unhealthy diet (3-5). This thesis reported that patients' motivational patterns are associated with their physical activity and dietary quality, which tentatively indicates that targeted motivational counseling might be effective in order to achieve or consolidate a healthy lifestyle. However, existing evidence also indicated that improving cognitive impairment (CI) or cognitive functioning could be effective to this end. Unfortunately, CI remains an under-recognized manifestation of COPD andour working memory training (WMT) intervention could not improve overall cognitive functioning or adherence to a healthy lifestyle.

This chapter will discuss how the clinical recognition and assessment of CI in COPD could be improved, and it will discuss various other potentially effective strategies to improve cognitive functioning in patients with COPD and their adherence to a healthy lifestyle.

Cognitive impairment as under-recognized COPD manifestation

CI is highly prevalent in COPD, with a prevalence of around one in three (6), and cognitive performance substantially influences patients' daily lives. Memory, cognitive flexibility and visual processing are related to self-management skills, such as the ability to adhere to one's medication regime (7, 8), and CI in general is associated with increased risk for exacerbations and hospitalizations (9-11). Nevertheless, many patients and health care professionals under-recognize CI as a comorbidity of COPD (12). Even the GOLD guidelines (13), outlining the standards in COPD management, do not address cognitive functioning and its influence on disease management and daily-life outcomes.

Cognitive screening could be a valuable addition to COPD management, as it could enable timely intervention and prevention of the harmful consequences of CI. Cognitive screening is not time- or labor-intensive: instruments such as the Mini-Mental State Examination (MMSE) (14), the Montreal Cognitive Assessment (MoCA) (15) or the Addenbrooke's Cognitive Examination-Revised (ACE-R) (16) take less than ten minutes to administer and are sensitive to detect CI in patients with COPD. They are easy to score and to interpret because of clear cut-off

values for CI. Moreover, patients with COPD themselves do not regard cognitive screening as a strange addition to standard diagnostics (12).

Nurses or lab technicians could periodically conduct this cognitive screening, for instance in conjunction with patients' routine lung function evaluation, which usually takes place biannually in The Netherlands. Cognitive screening could be followed up in a similar way as spirometric evaluation: if it reveals impairment or decline, the general practitioner or chest physician can be informed and advised to refer the patient for more comprehensive investigation. Cognitive abnormalities could lead, for example, to referral to a memory clinic in the hospital, which can administer comprehensive neuropsychological assessment.

Metabolic syndrome and sarcopenia as potential indications for screening

Multifactorial involvement of disease-specific determinants, comorbidities and unhealthy lifestyle behaviors in the emergence of CI in COPD makes some of these factors potentially useful to target screening at specific at-risk subgroups of patients with COPD. Metabolic abnormalities such as the metabolic syndrome (MetS) and sarcopenia, for instance, are common conditions in patients with COPD compared to healthy controls (17, 18) and have been related to the prevalence of CI in non-COPD populations (19-23). However, our research showed no independent contribution of MetS and sarcopenia towards CI in patients with COPD who were referred for pulmonary rehabilitation (PR). This could be specific for this COPD subgroup and different in population-based studies. Future research is furthermore indicated to identify the potential of other comorbidities or lifestyle factors in the risk screening for CI in COPD.

Alternatively, COPD may have a much larger effect on cognitive performance than MetS and sarcopenia. The impact of COPD on cognitive functioning might therefore overshadow the (perhaps negligible) impact of MetS and sarcopenia. This conjecture is supported by the relatively high prevalence of CI in the patients who were investigated in our research (almost 40 percent), regardless of MetS or sarcopenia status. This prevalence was determined by comparing the patients' cognitive performance to that of non-COPD controls. COPD-general effects on cognitive performance could be biologically mediated by accelerated ageing. Accelerated biological ageing is a hallmark of COPD (24) and has also been related to poorer cognitive performance (25-27) and accelerated cognitive decline (26, 28, 29) in otherwise healthy participants.

Improving cognitive performance

In case CI is diagnosed, it should ideally be treated, especially in light of the serious consequences of CI in patients with COPD. We chose to administer WMT as the role of WM underlying general cognition (30) made it a promising target to improve overall cognitive performance. However, the results of the Cogtrain trial as well as earlier WMT interventions were disappointing. In the Cogtrain trial as well as earlier studies, WMT appeared to be able to improve cognitive performance on the initially trained tasks, but near transfer (i.e., towards comparable cognitive tasks) was scarce and far transfer (i.e., towards unrelated cognitive tasks) was virtually non-existent (31-33). To date only one study investigated another type of cognitive training in patients with COPD. This intervention, targeting attention and logical-deductive thinking with a lower training load than the Cogtrain trial, was also ineffective (34).

Based on this evidence, WMT cannot be recommended for use in future studies or clinical practice, at least not as a stand-alone intervention in its current form.

Targeting cognitively well- or poorly-performing patients: who benefits?

Baseline cognitive performance in the Cogtrain trial was highly variable. The median ACE-R score of 88 was relatively poor, but the highest-performing quartile of patients showed normal cognitive performance with scores above 94. This variability could also explain the non-significant results of the trial, as WMT might have different effects on patients with poor and good baseline cognitive performance. This has not been investigated in the Cogtrain trial, as the subgroups resulting from its relatively small sample size would be too small to draw any meaningful conclusions.

On the one hand, cognitively well-performing patients might have diluted effects that were present in more poorly-performing ones. Transfer from improved performance on one cognitive task towards another is unlikely to occur if participants do not improve on the trained tasks (35), and the available room for improvement is largest in cognitively poor patients. On the other hand, poorly performing patients might also have diluted effects that were present in the better ones. Plasticity is a prerequisite for learning and transfer, and it could be argued that the potential for cognitive plasticity (i.e., the ability to learn and use multiple new cognitive strategies) and neural plasticity (i.e., cerebral physiological adaptability) is likely largest in those with better initial cognitive performance.

Daily-life cognitive stimulation

Improving cognitive functioning does not require standardized or formalized cognitive training. Cognitive stimulation associated with daily-life activities such as playing chess (36), completing sudokus (37) or even the degree of social contact (38, 39) are also associated with improved cognitive functioning. These activities have multiple advantages over formalized cognitive training: their structure is less rigid and they have a much more 'gamified' character, so patients will likely be more willing to engage in them and adhere to them. They are easy to incorporate into daily life. This increases the likelihood that these activities become a habit, which makes it easier to adhere to them in the longer term.

Physical activity, exercise training and the muscle-brain axis

Physical activity and exercise training are among the most effective ways to improve brain health and cognitive functioning (40-42). These effects are mediated among others by increased cardiac output, social interaction in the case of group exercise (43) and extensive muscle-brain crosstalk.

This crosstalk takes place among others through the effects of exercise-induced release of myokines such as cathepsin B or FNDC5 (44). These and other factors mediate the upregulation of neurotransmitters such as brain-derived neurotrophic factor (BDNF), vascular endothelial growth factor (VEGF) and insulin growth factor-1 (IGF-1) (44-46). These neurotransmitters improve brain health by facilitating neurogenesis, neuronal survival, differentiation, myelination and memory formation (43, 47). A large part of these effects takes place in the hippocampus (44, 48), which is the primary brain area responsible for memory formation.

The kynurenine pathway also plays a key role in this muscle-brain crosstalk. This pathway mainly converts tryptophan into kynurenine and further into quinolinic acid (an N-methyl-D-aspartate receptor [NMDAR] agonist which induces excitotoxicity in the brain) or kynurenic acid (an NMDAR antagonist with neuroprotective properties) (49, 50). Quinolinic and kynurenic acid cannot cross the blood-brain barrier, but kynurenine can (51). Kynurenine should therefore ideally be metabolized in the periphery, to prevent it from crossing the blood-brain barrier and being metabolized into neurotoxic compounds in the central nervous system. This risk is especially present in patients with COPD, because inflammation, which is systemically heightened in patients with COPD (13), promotes the conversion of kynurenine into quinolinic acid instead of kynurenic acid (50). Accordingly, the

kynurenine-to-tryptophan ratio (KTR) has been negatively related to cognitive performance (52).

Exercise promotes peripheral kynurenine metabolism (and therefore potentially benefits cognitive performance) through increasing PGC-1α and PPARα/δ expression in the skeletal muscle (53). This leads to increased skeletal muscle kynurenine aminotransferase (KAT) expression (49, 53), which in turn promotes the conversion of kynurenine into kynurenic acid (53). Indeed, the peripheral KTR of healthy young adults was significantly lower 1 hour after exercise compared to baseline (49). Indirectly improving cognitive performance in COPD via such exercise-induced muscular improvements makes sense in theory, as their plasma kynurenine levels are significantly higher than those of healthy controls and their skeletal muscle KAT expression is significantly lower (54).

Nutritional supplementation, dietary management and the gut-brain axis

Brain health and cognitive performance may also be improved by targeting the gut microbiome. The gut microbiome communicates with the brain through the 'gut-brain axis' (55). This axis consists of many different pathways. It releases pro- and anti-inflammatory cytokines such as interleukin-1 and -6, which modulate the activity of the hypothalamic-pituitary-adrenal gland (HPA) axis (55). It secretes short-chain fatty acids which activate microglial cells that have anti-inflammatory effects in the brain (56). It modulates the activity of the vagus nerve, which is associated with improved cognitive functioning in the general population when it is done exogenously (57, 58), and it also regulates the levels of (precursors of) important neurotransmitters such as serotonin, gamma aminobutyric acid (GABA), noradrenalin, dopamine and acetylcholine (55, 56).

The composition of the gut microbiome and the functioning of the gut-brain axis can be improved by administering so-called 'psychobiotics'. Psychobiotics are "pre- and probiotics that, ingested in appropriate quantities, have a positive mental health benefit" (55). Fructooligosaccharides (FOS) and galactooligosaccharides (GOS), for instance, stimulate the growth of intrinsic commensal microbiota, which are bacteria in the gut that positively influence the diversity of the gut microbiome (55). The current evidence for the beneficial effects of psychobiotics is strongest for stress, anxiety and depression (59); surprisingly, there is a paucity of research into the effects of psychobiotic supplementation on cognitive performance. Future studies may therefore further investigate this topic, and whether and how psychobiotic supplementation is related to the composition and diversity of the gut microbiome.

Various nutrients can also modulate the gut microbiome and gut-brain axis. The NUTRECOVER trial, which is currently ongoing within the department of respiratory medicine at Maastricht University, will unravel the effects of a nutritional supplement containing tryptophan, vitamin D, omega-3 polyunsaturated fatty acids (PUFA) and prebiotic fibers on among others cognitive performance in patients with COPD who have been hospitalized with an acute exacerbation. This 'cocktail' may simultaneously moderate the kynurenine pathway and the gut-brain axis. The anti-inflammatory properties of PUFAs, such as eicosapentaenoic acid (EPA) or docosahexaenoic acid (DHA) (60), could shift the metabolism of the supplemented tryptophan and subsequently kynurenine in the brain towards kynurenic acid instead of quinolinic acid. Additionally, the prebiotic fibers may improve the composition of the gut microbiome (59), which might in turn also benefit the kynurenine pathway (61). Clinical trials have already shown positive effects of PUFA and dietary fiber supplementation on cognitive performance in cognitively healthy elderly and those with mild CI (62-64). A lower vitamin D status has been associated with poorer cognitive performance in (older) adults without dementia, although the benefits of supplementing it are still unclear (65).

Consuming a healthy diet, such as the Mediterranean diet (66-70), a prudent diet (71), the Dietary Approaches to Stop Hypertension (DASH) diet (69, 70) and the Mediterranean-DASH Intervention for Neurodegenerative Delay (MIND) diet (70), can also improve cognitive performance. The Mediterranean diet and the prudent diet are characterized by high fruit, vegetable, fish, wholegrain, oil, legume, nut and low-fat dairy intake while limiting the intake of red meat, sweets, sugar-containing beverages, fat and cholesterol (69, 71). The DASH diet is largely similar but places a larger emphasis on low-fat dairy and low dietary sodium intake and alcohol abstinence (69), whereas the MIND diet combines the Mediterranean and DASH diets and emphasizes plant-based foods over animal foods and foods high in saturated fat (70).

Nootropics

Nootropics are pharmacological substances that can be used to enhance cognitive performance, such as (ar)modafinil and methylphenidate, but also caffeine or nicotine (72-74). They are popular in the general population (mainly among students in order to enhance their academic performance). Taking nootropics is a much easier way to enhance cognitive performance compared to strategies such as exercise or consuming a healthy diet, but it is associated with considerable drawbacks. Firstly, substances such as methylphenidate or modafinil (primarily indicated in The Netherlands for attention deficit / hyperactivity disorder and for narcolepsy, respectively (75, 76)) were not developed with the aim of cognitive

enhancement in mind. As such, the evidence base for their cognitive performance-enhancing properties is weak, especially in people with comparable demographical and pathophysiological characteristics as typical patients with COPD. Most meta-analyses and systematic reviews have investigated their effects in younger adults or in patients with traumatic brain injury (77, 78). Secondly, nootropics can have unintended and undesirable side effects such as headaches or insomnia (75, 76). Thirdly, they should be very carefully administered as overdosing can lead to suboptimal cognitive performance (79) and harmful effects on cerebral functioning (80). Therefore, using nootropics with the sole aim of cognitive enhancement (i.e., without any other indication) cannot be recommended.

One class of medication that might be feasible as a nootropic in patients with COPD are phosphodiesterase (PDE)-4 inhibitors such as roflumilast. They have been shown to improve cognitive performance in animal models of Alzheimer's disease (81) and chronic cerebral hypoperfusion (82). Acute administration of 100µg (but not 250, 300, 500 or 1000µg) roflumilast significantly improved immediate recall memory performance in healthy young adults (83) and delayed recall memory performance in healthy older adults (84).

Roflumilast has recently been indicated in The Netherlands to treat patients with severe COPD (FEV_1 < 50% predicted) who suffer from frequent exacerbations despite optimal triple therapy (85). Its potential to simultaneously improve the health status and cognitive functioning of patients with COPD would make it a promising intervention. Moreover, it is relatively cheap, with an estimated price per day of €1.74 (85). However, although acute administration of the recommended therapeutic dose for COPD (500µg) tended to lead to better cognitive performance compared to placebo in participants without COPD, these differences were not significant (83, 84). The effects of long-term roflumilast administration on human cognitive performance have not been investigated to our knowledge. Hence, whether roflumilast administration alone or as part of standard COPD management could contribute to cognitive improvement remains to be investigated.

Pulmonary rehabilitation

PR is also prescribed to patients with severe COPD as part of standard disease management (86). PR includes many components with proven benefits on cognitive performance, such as exercise training and nutritional support (86), and the available evidence indeed provides tentative indications of favorable effects of PR on cognitive performance (43, 87-89). The necessary investment in terms of money, time and effort do not make PR a viable option to improve cognitive performance of patients with COPD on a large scale, but it could benefit those

patients who are referred for PR based on the existing indications. Moreover, the likely poor cost-effectiveness of PR to improve cognitive functioning does not negate the fact that incorporating its key elements, such as physical activity, exercise and dietary improvement, into daily life will likely benefit cognitive performance, as discussed above. Future research should expand on the existing evidence base with methodologically stronger studies. They should for instance, in contrast to earlier studies, include a non-PR control group (43, 87) and include a broader sample of patients than only certain subsets such as those who have undergone a lung transplantation (89).

PR is a very effective intervention to improve health outcomes, but its transfer into an actual healthier lifestyle after completion of the program and after the associated support and structure are taken away, is only poor (90). Interventions targeting patients' daily lives in the first place may be more effective.

Comprehensive lifestyle interventions

Many modifiable lifestyle factors influence cognitive performance. The Dutch Alzheimer Centre lists mental and physical inactivity, smoking, depression, overweight, hypertension and diabetes as important risk factors to develop dementia (91). Targeting one factor in an intervention while leaving all others constant therefore likely only has a small effect on cognitive performance. Instead, interventions likely become more effective as more factors are targeted.

However, in spite of this enhanced effectiveness in theory, the current empirical evidence for such multidomain interventions is mixed. Over the past decade, three large-scale studies have investigated the potential of comprehensive lifestyle interventions to diminish the risk of developing dementia: the Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER) (92), the preDIVA study (93) and the Multidomain Alzheimer Preventive Trial (MAPT) (94). The 2-year FINGER strategy consisted of nutritional management, exercise training, cognitive training and vascular risk monitoring. The 6-year preDIVA study combined usual cardiovascular care with tailored lifestyle advice based on motivational interviewing principles; the 3-year MAPT trial offered cognitive training, physical activity, nutritional supplementation and educational sessions. The FINGER trial was able to prevent cognitive decline to a significantly greater degree than general health advice, but the preDIVA and MAPT studies did not lead to significant changes in cognitive decline compared to placebo groups. In conclusion, there is a clear need for future studies to investigate the potential of such multidomain interventions, and to identify which components are effective to which degree.

Working memory training and adherence to a healthy lifestyle

In this thesis WMT was hypothesized to be able to contribute to a healthier lifestyle through its ability to increase cognitive control (95, 96). This would enable patients to inhibit automatic responses in favor of more opportune controlled ones (97). However, the Cogtrain trial showed no effects of WMT on adherence to a healthy lifestyle, the recall of prespecified healthy lifestyle goals or motivation towards a healthy lifestyle.

One potential explanation for these non-significant results is that transfer from improved performance on one cognitive domain to other cognitive domains is already scarce (31, 32). Transfer towards healthy lifestyle outcomes would have to reach even further. All of these outcomes are determined by a potentially endless number of pathways involving motivational, environmental (e.g., the weather, social support, financial issues) and health-related factors (e.g., disease progression). WMT-induced improved cognitive control may contribute to adherence to a healthy lifestyle, but it is not a panacea.

Secondly, the positive effects of earlier studies investigating the effects of WMT on healthy lifestyle outcomes or stress susceptibility were largely found on lab-based parameters or tasks (such as a bogus taste test in participants with overweight or metabolic parameters in those with type 2 diabetes) instead of actual healthier lifestyles (i.e., weight loss or disease management) (95, 98). Even studies which selectively included specific subgroups of participants who stood to gain a lot by participating, such as people with overweight in studies with weight loss as a primary outcome (99) or heavy drinkers in a study aiming to reduce substance abuse (100), were largely ineffective. The one recent study investigating the effects of WMT on stress responses found positive results on the biological response to stress (measured by cortisol levels) but did not include a measure of subjective stress perception (101).

Thirdly, increasing cognitive control might not be necessary or sufficient to establish a healthy lifestyle. It might not be sufficient because a large proportion of patients with COPD appear not to know what is and is not healthy: 30% of them qualify as being health illiterate (102, 103). Future studies and clinical efforts may therefore have to add educational components in order to enable patients to keep the right information in mind. However, the effectiveness of combining only WMT and education is doubtful (95), implying that these components will also have to be part of a more comprehensive interventional strategy.

Combining education, WMT and additional interventional components is a highly cumbersome way to achieve a healthier lifestyle. All of this might not be necessary in the first place, because it could simply and effectively be bypassed using a technique called 'nudging' (104). . Nudging consists of altering certain aspects of people's environment with the aim of automatically guiding them towards a certain choice even though they retain the freedom to choose any number of other options (104). It therefore minimizes the necessary involvement of cognitive control, instead of maximizing its capacity. Nudging can be very easy and subtle, and it can unconsciously change behavior: it can consist of placing the fruit and vegetables department immediately at the entrance of a supermarket and making it impossible not to pass through it before reaching other departments with unhealthier items. Importantly, customers retain full freedom to pick unhealthy products, but the likelihood of them buying fruit and vegetables is much larger compared to when the fruit and vegetables department is located in the middle or the back of the store. Its non-coercive nature also makes nudging much more likely to be effective, also in the longer term, compared to educational or prescriptive approaches telling you what you 'should' or 'should not' do (105, 106).

General conclusion

CI is an important comorbidity of COPD, which should be better recognized and dealt with in the clinic. WMT as single intervention does not improve cognitive performance in COPD. Future initiatives to improve cognitive performance in patients with COPD should focus on alternative, preferably multimodal, interventions.

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Summary

Chronic obstructive pulmonary disease (COPD) is a high-burden chronic respiratory disease. It is currently the third most common cause of death worldwide, with an estimated 3 million deaths in 2016. Traditional interventions to improve the health status of patients with COPD, such as supervised pulmonary rehabilitation (PR) programs, are effective in the short term but often do not translate into a healthier and generally more active lifestyle after completion of the program. Promising additional or alternative approaches to maintain or improve health status of COPD patients include motivational counseling towards a healthy lifestyle, targeted nutritional intervention or working memory training (WMT).

Cognitive impairment (CI) is a common extrapulmonary manifestation of COPD, and is evidenced for example by memory loss or reduced speed of thinking. CI is a problem in itself, but also affects overall health status of patients with COPD and may influence their ability to adhere to a healthy lifestyle.

The main aim of this thesis was therefore to investigate determinants of cognitive performance in patients with COPD and the potential efficacy of WMT next to motivational regulations in increasing patients' adherence to a healthy lifestyle.

Chapter 2 reports the long-term results of the randomized, placebo-controlled NUTRAIN trial. This study investigated the cost-effectiveness of a nutritional management strategy in patients with COPD and low muscle mass (often referred to as sarcopenia). The strategy consisted of targeted nutritional supplementation (leucine, polyunsaturated fatty acids and vitamin D) in a medical drink and dietary counselling during a 4-month outpatient PR program and a subsequent 8-month maintenance phase. Relative to usual care (PR without follow-up intervention) physical capacity increased in both groups, but the nutritional management approach ameliorated plasma levels of the supplemented nutrients, prevented unintended weight loss, and positively influenced daily physical activity and generic health.

Chapter 3 investigates whether motivational regulations are related to healthy lifestyle behaviors (physical activity and adherence to a healthy diet) and the responsiveness thereof after an outpatient PR program. Levels of identified motivation (i.e., performing an action because it is valued as personally important to someone) predicted dietary quality change during PR and its levels after PR; levels of introjected motivation (i.e., performing an action out of fear of the shame associated with not doing it) predicted change in physical activity levels during PR and its levels after PR.

Chapter 4 provides a narrative review of the initial knowledge base around CI in COPD. Based on the current literature, several disease-specific factors, comorbidities and unhealthy lifestyle factors may contribute to the emergence of CI in COPD, which affects around one in three patients. A diffuse pattern of cognitive domains is affected, in contrast to disease-specific patterns such as the selective loss of memory (but not other cognitive domains) in Alzheimer's disease. These impairments have a detrimental impact on patients' self-management abilities, health outcomes, ability to engage in activities of daily living and quality of life, while increasing their hospitalization risk.

Chapter 5 investigates whether the presence of the metabolic syndrome or sarcopenia is related to an elevated prevalence and/or different pattern of CI in patients with COPD referred for PR. These conditions are more common in COPD than in healthy controls and adversely affect health status and survival. COPD patients with one of these comorbidities might be especially vulnerable to develop CI, as these conditions have been independently associated with poor cognitive functioning in non-COPD populations. In the studied COPD population referred for PR, the prevalence of metabolic syndrome (54.7%) and sarcopenia (30.0%) was high, but not associated with a higher prevalence of CI.

Chapter 6 reports the results of the randomized, placebo-controlled Cogtrain trial. In this trial a 12-week home-based working memory training (WMT) program was administered, followed by a 12-week maintenance program. The efficacy of WMT to establish and maintain improvements in cognitive performance, adherence to a healthy lifestyle and cognitive stress susceptibility was investigated in patients with COPD. Although the intervention improved performance on the actual (working memory) tasks that were used for training, these improvements did not generalize to other cognitive performance domains. The WMT did not improve adherence to a healthy lifestyle or cognitive stress susceptibility either. These results indicate that WMT is not an effective way to improve cognitive performance and potentially related healthy lifestyle behavior in patients with COPD.

Chapter 7 positions the results of the current thesis in a broader scientific and clinical perspective, with particular emphasis on cognitive functioning in COPD and on the potential efficacy of interventions to improve cognitive performance and adherence to a healthy lifestyle in patients with COPD.

The overall results of the current thesis indicate that CI is an important comorbidity of COPD, which should be better recognized and dealt with in clinical care. CI has an independent substantial detrimental impact on daily-life functioning and health outcomes of patients with COPD. Metabolic abnormalities (i.e., the

metabolic syndrome and sarcopenia) do not appear to be useful screening factors for CI in patients with COPD. WMT did not improve cognitive functioning or adherence to a healthy lifestyle. However, motivational regulations were shown to be potentially effective interventional targets to establish and maintain a healthy lifestyle following PR.

Samenvatting

COPD is een veelvoorkomende en ernstige chronische longziekte, die momenteel de op twee na meest voorkomende doodsoorzaak wereldwijd is. In 2016 was COPD naar schatting verantwoordelijk voor 3 miljoen doden. Gangbare niet-medicamenteuze interventies om de algemene gezondheid van patiënten met COPD te verbeteren, zoals longrevalidatie, zijn effectief op korte termijn, maar beklijven vaak niet op de langere termijn via een gezondere leefstijl. Een gerichte voedingsaanpak, motivationele counseling en werkgeheugentraining zijn veelbelovende aanvullende of alternatieve behandelingen om de gezondheid en leefstijl van patiënten met COPD te verbeteren.

Verminderd cognitief functioneren, zoals bijvoorbeeld geheugenverlies of een vertraagd denkvermogen, komt vaak voor bij COPD. Deze cognitieve beperkingen beïnvloeden de algehele gezondheid van patiënten met COPD en verminderen hun vermogen om gezond te leven.

In deze thesis is nader onderzoek verricht naar de risicofactoren voor cognitief functieverlies bij COPD alsmede de trainbaarheid van het cognitief functioneren middels werkgeheugentraining. Daarnaast is onderzocht of deze training naast een doelgerichte voedingsinterventie en inzicht in verschillende vormen van motivatie kan bijdragen aan een gezondere leefstijl van patiënten met COPD.

Hoofdstuk 2 rapporteert de langetermijnsresultaten van de gerandomiseerde, placebo-gecontroleerde NUTRAIN-trial. De interventiegroep ontving een medische drinkvoeding die verrijkt was met leucine, meervoudig onverzadigde vetzuren en vitamine D gedurende een 4 maanden durend poliklinisch revalidatieprogramma en counseling middels motivationele interviews tijdens de daaropvolgende onderhoudsfase van 8 maanden. Deze interventie verbeterde na 12 maanden de plasmaniveaus van de gesuppleerde nutriënten, voorkwam gewichtsverlies en verminderingen in fysieke activiteit en algemene gezondheid, en was kosteneffectief. Een verbeterde fysieke capaciteit na de longrevalidatie bleef behouden voor zowel de interventiegroep als de controlegroep.

Hoofdstuk 3 onderzoekt of verschillende vormen van motivatie voor het naleven van een gezonde leefstijl daadwerkelijk gerelateerd zijn aan een gezonde leefstijl (fysieke activiteit en een gezond dieet) tijdens en na afloop van een poliklinisch longrevalidatieprogramma. Dit werd onderzocht in het kader van de NUTRAIN trial. Niveaus van geïdentificeerde motivatie (m.a.w. een actie uitvoeren omdat die aansluit bij iemands persoonlijke waarden) waren gerelateerd aan de verandering in de kwaliteit van het dagelijkse voedingspatroon tijdens en na afloop van longrevalidatie; niveaus van geïntrojecteerde motivatie (het uitvoeren van een actie uit angst voor de schaamte die gerelateerd is aan het niet uitvoeren ervan)

waren gerelateerd aan de verandering in fysieke activiteit tijdens en na afloop van de revalidatie.

Hoofdstuk 4 betreft een narratieve review over de bestaande literatuur over verminderd cognitief functioneren in patiënten met COPD. Dit hoofdstuk toont aan dat enkele ziekte-specifieke factoren, comorbiditeiten en een ongezonde leefstijl kunnen bijdragen tot het ontstaan van cognitieve beperkingen in COPD. Deze beperkingen treffen ongeveer een op de drie patiënten. Veel verschillende cognitieve domeinen kunnen aangedaan worden maar er bestaat geen ziekte-specifiek patroon zoals het geheugenverlies dat karakteristiek is voor de vroege stadia van de ziekte van Alzheimer. Cognitieve beperkingen hebben een negatief effect op de gezondheid, het vermogen tot zelfmanagement, het dagelijks leven en de kwaliteit van leven van patiënten met COPD. Bovendien verhogen cognitieve beperkingen het risico op een ziekenhuisopname.

Voortbouwend op deze review is in **Hoofdstuk 5** onderzocht of de aanwezigheid van het metabool syndroom of sarcopenie gerelateerd is aan een hogere prevalentie en/of een verschillend patroon van cognitieve beperkingen in patiënten met COPD die verwezen waren voor longrevalidatie. Deze metabole aandoeningen komen vaker voor in COPD dan in gezonde controles, en we weten uit eerder onderzoek dat beide metabole condities op zichzelf geassocieerd zijn met een verminderd cognitief functioneren. Het metabool syndroom en sarcopenie hadden een hoge prevalentie in onze bestudeerde COPD-populatie (respectievelijk 54.7% en 30.0%), maar ze bleken niet gerelateerd te zijn aan een hogere prevalentie van cognitieve beperkingen. Dit zijn daarom geen bruikbare indicaties voor aanvullende cognitieve screening.

Hoofdstuk 6 toont de resultaten van de gerandomiseerde, placebo-gecontroleerde Cogtrain-trial. Dit onderzoek bestond uit een 12-weekse werkgeheugentraining, gevolgd door een 12-weeks onderhoudsprogramma, in patiënten met COPD. Het doel van het onderzoek was om verbeteringen te bewerkstelligen en te consolideren in het cognitief functioneren, de leefstijl en de vatbaarheid voor cognitieve stress. Hoewel het functioneren op de getrainde (werkgeheugen-)taken duidelijk verbeterde, waren er geen verbeteringen te zien op andere cognitieve domeinen na de training. De interventie had ook geen effecten op de andere onderzochte parameters. Werkgeheugentraining lijkt dus geen effectieve manier om het cognitief functioneren en daarmee samenhangende leefstijlaspecten van patiënten met COPD te verbeteren.

Hoofdstuk 7 plaatst de resultaten van het onderzoek in een breder wetenschappelijk en klinisch perspectief, met een focus op andere benaderingen

om het cognitief functioneren en een bestendige gezondere leefstijl te verbeteren bij patiënten met COPD.

Impact

Chronic obstructive pulmonary disease (COPD) is one of the highest-burden chronic diseases worldwide. Lung function impairment is characterized by airflow limitation that is usually progressive and largely irreversible (1). COPD is a substantial cause of disability and mortality: 299 million people worldwide were estimated to suffer from the disease in 2017 and COPD was responsible for 3 million deaths in 2016, making it the third most common cause of death worldwide (2).

Although COPD is primarily a lung disease, various manifestations outside the respiratory system are common, including metabolic abnormalities (3, 4), muscle dysfunction (5) and cognitive impairment (CI) (6). CI worsens patients' quality of life (7, 8) and health outcomes (9, 10), it decreases their ability to engage in activities of daily living (11) and it increases their risk of hospitalization (12). All of this contributes to a vicious cycle in which patients' health status deteriorates even further, and to a considerable economic burden for society (13, 14). It is therefore very important to optimally manage COPD from a holistic perspective, consider CI as comorbidity and to assist patients in attaining and maintaining a healthy lifestyle. This thesis investigated determinants of cognitive performance in patients with COPD and the potential efficacy of working memory training (WMT) and nutritional management next to motivational regulations in increasing patients' adherence to a healthier lifestyle.

Relevance for patients

The results of this thesis are very relevant to patients with COPD. Awareness regarding the adverse impact of their disease and leads for improvement might translate into their health status and wellbeing. Improved prospective memory could for example improve self-management and treatment adherence. Improved executive functioning could enhance self-control, enabling patients to resist tempting unhealthy lifestyle choices in favor of more controlled and healthier ones. The WMT that we developed and evaluated as single intervention was unable to improve overall cognitive functioning or adherence to a healthy lifestyle. Nevertheless, interventional modalities, such as daily-life cognitive stimulation (e.g., playing chess (15), completing sudokus (16) or engaging in social interaction (17, 18)) physical activity (19, 20) and dietary improvement (21, 22), have been shown to benefit cognitive performance in non-COPD populations and are recommended, also in light of other common comorbidities in COPD.

Relevance for clinical practice

Raising awareness for cognitive impairment in COPD and interventions (also) targeting cognitive functioning in these patients is very relevant for caregivers. The prevalence of CI was particularly high in patients referred for pulmonary rehabilitation (PR) compared to earlier prevalence estimates in stable patients in population studies (6). This, and the fact that CI has been related to adverse health outcomes including the likelihood of dropping out of PR (23), underlines the importance for PR providers to recognize the possible presence of CI in their patients and to tailor educational programs to patients' cognitive capacities.

Furthermore, new insights in specific motivational regulations associated with indicators of adherence to a healthy lifestyle (i.e., physical activity and dietary quality) are important to consider in refining COPD-specific lifestyle counseling interventions.

Relevance for society

A main aim of this thesis was to determine the health and lifestyle benefits of the investigated interventions. WMT was ineffective, but targeted nutritional management improved patients' health status at an increase of costs that might be considered acceptable for patients with a high disease burden. Moreover, motivational interventions, if proven feasible as discussed above, might cost-effectively improve patients' lifestyle, health status, quality of life and functional capacities as well. This enables patients to live more meaningful lives for a longer period of time, for instance by prolonging their ability to work. Furthermore, it might decrease health care expenditure and the COPD-associated disability burden. Both are relevant for society, as rising health care costs present a large and growing economic burden and COPD is the fifth-leading cause of disability-adjusted life years (DALYs) worldwide (24).

Relevance for commercial parties

Motivational counselling does not have to remain confined to health care professionals. In fact, counselling by commercial parties would take work away from health care professionals, which would alleviate the growing work pressure and financial burden on the health care system.

Incorporating counselling into an e-health application could reduce the workload associated with counselling even further. Various applications have been developed over the past years to improve chronic disease management with promising results on health outcomes, such as myIBDcoach (25, 26) for inflammatory bowel disease and SanaCoach COPD for COPD (27). Counselling could even take place entirely virtually. Habtic, an app developed to improve the lifestyle of corporate employees, already uses such virtual, yet highly realistic, avatars.

The NUTRAIN trial showed that nutritional supplementation can improve the overall health status of patients with COPD in a cost-effective manner. Further developing medical foods and/or supplements, aimed at improving physical capacity and health status but also building forth upon promising results regarding their benefits on cognitive functioning (28, 29), for instance, could therefore be promising for commercial parties.

Developing WMT modalities and marketing them as games has been an important focus of industry in the past 20 years. Although these games are often supported by claims that their effectiveness has been proven, independent investigations routinely indicate they do not improve cognitive or real-life task performance (30-32). The results of the current thesis also indicate that further developing WMT applications is likely not worthwhile.

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Curriculum vitae

Martijn van Beers was born on June 3rd, 1994, in Veldhoven, The Netherlands. He followed prepratory scientific education (VWO) at the 'Heerbeeck College' secondary school in Best (Noord-Brabant, The Netherlands). After graduating in 2012, he successfully completed the bachelor program in Psychology at Tilburg University in 2015, where he wrote his thesis under the supervision of dr. Ruth Mark. Subsequently, he obtained a master in Neuropsychology at Maastricht University in 2016. He wrote his master thesis at Hasselt University (Belgium) under the supervision of dr. Ellen Jongen en dr. Judith Urlings.

In December 2016 he started his PhD research at the Department of Respiratory Medicine at Maastricht University, where he conducted the research described in this thesis, investigating determinants of cognitive performance in patients with chronic obstructive pulmonary disease and the potential efficacy of working memory training next to motivational regulations in increasing patients' adherence to a healthy lifestyle. He performed this research under the supervision of prof. dr. ir. Annemie Schols and dr. Harry Gosker. During this period he also presented his work at various national and international conferences.

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